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SEPTEMBER 1943

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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ARCHIVES of INTERNAL MEDICINE

VOLUME 72 SEPTEMBER 1943 NUMBER 3

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VASCULAR DISEASE FOLLOWING TOXEMIA OF PREGNANCY (PREECLAMPSIA AND ECLAMPSIA)

OBSERVATIONS ON ITS CLINICAL COURSE

ABNER GOLDEN, M.D.

LEWIS DEXTER, M.D.

AND

SOMA WEISS, M.D.†

BOSTON

Most studies of persistent hypertension following toxemia of pregnancy have been of a statistical nature. We are not familiar with any work that describes in detail the clinical course. It is our purpose to do this in the hope that it will provide a better understanding of the nature and importance of this disease and stimulate others to amplify our observations. As we shall see, the clinical analogy of toxemia of pregnancy and its late effects to acute glomerulonephritis and its sequelae is striking despite a distinct difference in the etiologic and the pathologic aspects of the two diseases. It will, perhaps, be convenient to bear in mind this analogy in considering the material to be presented. It must be emphasized, however, that the two diseases are different etiologically and pathologically.

In this report we have confined our studies to cases in which toxemia of pregnancy was imposed on a previously normal cardiovascular renal system. Those cases in which toxemia aggravated preexisting hypertensive disease have not been included. We have encountered a sizable group of cases of hypertension in women in which it was suspected that the vascular disease originated in a toxemic pregnancy. For the purpose of this study, however, we have had to exclude many of these cases because of inadequate data. With 1 exception we have illustrated the important features of the course of post-toxemic hypertension by using only those cases in which the blood pressure and the urine were known to have been normal before or early in pregnancy, in which an accurate record of the toxemic course during pregnancy could be obtained and in which the blood pressure was determined and urinalysis was performed at frequent intervals post partum.

DEFINITION OF TOXEMIA OF PREGNANCY

Elsewhere two of us (L. D. and S. W.) [1] have defined toxemia of pregnancy (preeclampsia and eclampsia) as an acute vascular disorder characterized by the appearance in the latter half of pregnancy of (*a*) an abnormal elevation of blood pressure above the prepregnancy level (regardless of the presence or absence of

† Deceased.

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

This investigation was made possible by a grant from the John and Mary R. Markle Foundation and from the Armour Laboratories.

1. Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941.

hypertensive disease before the onset of pregnancy) or (*b*) an increase in the degree of albuminuria above the prepregnancy level in the absence of other obvious cause and (*c*) generalized edema in association with the foregoing changes in the majority of instances and (*d*) a rapid diminution of these abnormalities before or soon after delivery. Symptoms may or may not be present.

CRITERIA FOR THE DIAGNOSIS OF TOXEMIA OF PREGNANCY

Criteria for the diagnosis of toxemia of pregnancy have been discussed elsewhere at length.[2] The presence of hypertension or albuminuria in pregnancy does not necessarily imply the existence of toxemia. Diagnosis depends on recording a significant increase during the last half of pregnancy in blood pressure or degree of albuminuria above the level present before pregnancy, or during the first half. Determination of the presence or absence of hypertensive disease in the pregnant, as well as in the nonpregnant, woman is almost impossible in borderline cases, despite the introduction of ingenious diagnostic measures in recent years. It is not rare for the blood pressure to fall, particularly during the second trimester of pregnancy,[3] as in animals with experimental renal hypertension.[4] Should previous hypertension be mild, normal values may be recorded. The following case is an example of this. Hypertension persisted after toxemia in the second preg-

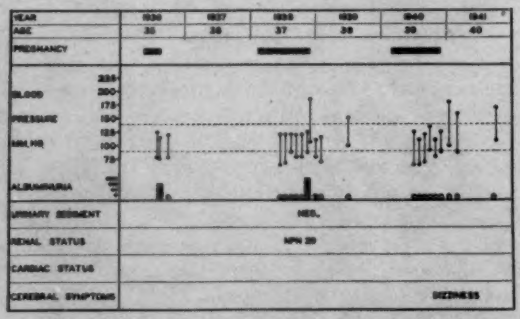

Fig. 1 (case 1).—Post-toxemic hypertension.

nancy. During the third pregnancy, two years later, the blood pressure was high normal on many occasions, and one month post partum definite hypertension was again present. Although it is infrequent to encounter normotension in a hypertensive patient during pregnancy, this case is included to illustrate the difficulty that may occur in evaluating measurements of blood pressure during gestation.

Case 1 (fig. 1).—B. D., a Negress, had no history of vascular or renal disease in the past. Her first pregnancy, in 1936 when she was 35 years old, was terminated at three months by a spontaneous abortion, at which time the blood pressure was 126 systolic and 80 diastolic and urinalysis revealed albumin (3 plus). One week after delivery, the blood pressure was

2. Dexter, L.; Weiss, S.; Haynes, F. W., and Sise, H. S.: Hypertensive Toxemia of Pregnancy: Preeclampsia and Eclampsia, J. A. M. A. **122**:145 (May 15) 1943. Dexter and Weiss.[1]

3. (*a*) Reid, D. E., and Teel, H. M.: Non-Convulsive Pregnancy Toxemias: Their Relationship to Chronic Vascular and Renal Disease, Am J. Obst. & Gynec. **37**:886 (May) 1939. (*b*) Dieckmann, W. J., and Brown, I.: Hypertension and Pregnancy, ibid. **36**:798 (Nov.) 1938. (*c*) Dexter and Weiss.[1]

4. Goldblatt, H., in discussion on Erickson, C. C., and Dill, L. V.: Observations on the Effects of Renal Ischemia in Pregnant Dogs and Rabbits, Am. J. Path. **15**:621 (Sept.) 1939. Dawson, J. R., Jr.; Cressman, R. D., and Blalock, A.: Experimental Hypertension and Pregnancy in Dogs, ibid. **17**:31 (Jan.) 1941. Corbit, J. D., Jr.: The Effect of Pregnancy upon Experimental Hypertension in the Rabbit, Am. J. M. Sc. **201**:876 (June) 1941.

122 systolic and 80 diastolic and the urine was free of albumin. The prepartal record of the second pregnancy, in 1938, follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1938	4	122/66	0	0
	5	120/68	0	0
	6	118/88	0	0
	7	120/80	0	0
	8	120/80	0	0
	9	184/104	++++	0

Eighteen days before delivery, the blood pressure was 126 systolic and 88 diastolic and the urine contained albumin (4 plus). The urinary sediment was normal. The blood pressure rose, reaching 184 systolic and 104 diastolic before the onset of labor, and large amounts of albumin persisted in the urine. Delivery was spontaneous and the fetus viable. Post partum her course was as follows:

Year	Time Post Partum	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1939	7 days	110/80	+	0
	12 days	115/70	0	0
	1 mo.	150/100	±	Headaches; dizziness
	6 mo.	150/100	0	0
1940	1 yr.	160/100	0	0
1941	2½ yr.	160/90	0	Dizziness
1941	3 yr.	170/110	0	0

A third pregnancy occurred in 1940, two years after toxemia. The prepartal record was as follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1940	4	126/64	0	0
	5	110/64	0	0
	6	122/70	0	0
	7	134/96	0	0
	8	110/80	0	0
	9	128/90	0	0

One month post partum, however, the blood pressure was 180 systolic and 100 diastolic and remained elevated for at least one year.

Occasionally, there is extreme difficulty in ruling out borderline hypertensive disease antedating pregnancy. This is illustrated by case 2. During the early months of pregnancy the blood pressure was consistently at the upper border of normal, although the patient was not definitely hypertensive at any time. Toxemia developed during the last trimester followed by definite persistent postpartum hypertension. It is possible that this patient had mild hypertension before pregnancy and that it became aggravated by toxemia.

Case 2 (fig. 2).—F. S. gave no history of vascular disease in the past. Her only pregnancy took place in 1933, when she was 30. The course during pregnancy is summarized below:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1933	3	134/86	0	Nausea; vomiting
	4	130/88	0	0
	5	125/76	0	0
	6	135/90	0	0
	7	160/105	0	0
	8	150/100	+	0
	9	164/110	+	0

During the ninth month she was hospitalized on three occasions for toxemia and received conservative therapy. Normal delivery followed the administration of castor oil. The postpartum course was as follows:

Year	Time Post Partum	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1933	7 days	150/94	0	0
	1 mo.	160/100	+	0
1935	1½ yr.	170/100	0	0
1936	2½ yr.	150/90	0	0
1937	4 yr.	180/100	0	0

These cases are designed to illustrate the difficulties involved in the diagnosis of hypertensive disease before pregnancy. In our opinion a sustained blood pressure of 130 to 140 mm. of mercury systolic and 85 to 90 mm. of mercury diastolic during

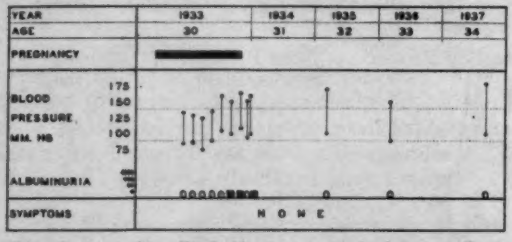

Fig. 2 (case 2).—Probable post-toxemic hypertension.

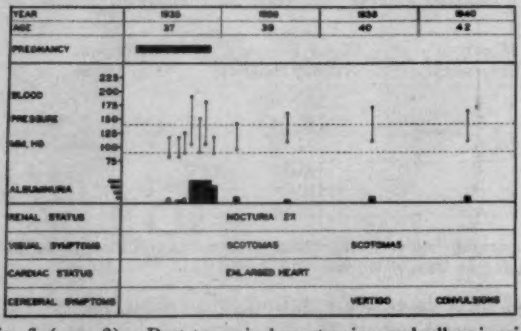

Fig. 3 (case 3).—Post-toxemic hypertension and albuminuria.

the early months of pregnancy is frequently indicative of borderline preexisting hypertensive disease, particularly in the age group under 30. The following case illustrates the development of toxemia of pregnancy and permanent hypertension in a patient whose urine and blood pressure were presumably normal before pregnancy.

Case 3 (fig. 3).—R. K., a Negress, had no past or familial history of vascular or renal disease. The first pregnancy, in 1930 when the patient was 32, terminated in a miscarriage after a fall. The second pregnancy, in 1935, was accompanied by mild nausea and vomiting during the early months. The prepartal record follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1935	4	120/80	0	0
	5	120/80	±	0
	6	125/90	0	0
	7	170/90	+	Fainting; dizziness
	7½	190/110	++++	
	8½	180/104	++++	

The patient was admitted to the hospital when she was seven and a half months pregnant, and with conservative therapy the blood pressure fell to 150 systolic and 100 diastolic. When she was eight and a half months pregnant, however, she was readmitted with severe preeclampsia; delivery was normal, and the fetus died a few days after birth. Post partum her course was as follows:

Year	Time Post Partum	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1935	5 days	124/80	+++	0
1935	10 days	118/88	+++	0
1936	3 mo.	140/94	+	0
1936	1 yr.	160/110	±	Scotomas; enlarged heart
1938	3 yr.	170/110	+	Scotomas; vertigo; nocturia with urination one to two times
1940	5 yr.	164/110	++; 0	

At the time of her last postpartum visit the patient had a convulsion lasting five minutes. Her husband revealed that she had had similar attacks every two to three months during the previous two years.

FACTORS INFLUENCING THE DEVELOPMENT OF PERMANENT POSTPARTUM VASCULAR DISEASE

It has been emphasized elsewhere [2] that by far the most important factor determining the persistence of postpartum hypertension is the duration of the hypertension or the albuminuria during pregnancy no matter how mild it is. Of decidedly secondary importance is the severity of the toxemia. Indeed, after eclampsia permanent vascular sequelae are uncommon.[5] We have advocated the termination of pregnancy after three weeks in cases in which toxemia does not respond to conservative therapy. Peckham [6] suggested termination of pregnancy after four weeks for this same reason. In the cases reported here it will be noted that the majority of women had preeclampsia, usually mild, and that it persisted for several weeks during pregnancy. Case 6 is exceptional in that permanent vascular damage followed eclamptic toxemia of short duration. Post-toxemic vascular disease is, therefore, one of the few types of hypertension which is often preventable.

EARLY STAGES OF POST-TOXEMIC HYPERTENSION

Although it is common for the blood pressure and the urine to return to normal within a few days or weeks after the termination of a toxemic pregnancy, hypertension and albuminuria in some instances may persist for months before disappearing. Such occurrences are not rare.

On the other hand, both blood pressure and urine may return to normal within a few days or weeks, and subsequently hypertension or albuminuria may reappear. How long this "latent" period may exist is a matter of conjecture and is extremely difficult to evaluate, as other causes may supervene to play a role in the production of subsequent vascular disease. We have seen instances in which hypertension did not reappear for as long as five years or more after toxemia of pregnancy,

5. Teel, H. M., and Reid, D. E.: Eclampsia and Its Sequelae: A Clinical Follow-Up of All Cases at the Boston Lying-In Hospital over a Twenty Year Period, Am. J. Obst. & Gynec. **34**:12 (July) 1937.

6. Peckham, C. H., Jr.: Time of Onset and Duration of the Toxemias of Late Pregnancy in Relation to the Development of Permanent Vascular Damage, Am. J. Obst. & Gynec. **42**:638 (Oct.) 1941.

but it is obviously impossible to decide what influence pregnancy had on the development of the hypertension under such circumstances. In the following case toxemia of pregnancy was characterized predominantly by albuminuria. The urine was free of protein six months post partum, but it contained albumin (2 plus) two years later.

CASE 4 (fig. 4).—H. C. had a past and a familial history which was noncontributory. Her only pregnancy, in 1938 and 1939 when she was 19 years old, can be summarized as follows:

Year	Month of Pregnancy	Blood Pressure, Systolic/Diastolic	Albumin in Urine	Symptoms
1939	5	110/60	0	0
	6	120/60	0; ±	0
	7	120/60	0	0
	8	130/70	0	Slight edema
	9	132/82	++	Moderate edema

The urinary sediment was normal at all times. There was a 71 pound (32 Kg.) gain in weight during pregnancy. Delivery, which was spontaneous and normal, was followed by a rapid

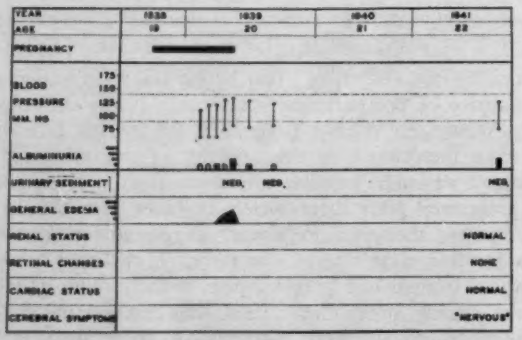

Fig. 4 (case 4).—Post-toxemic albuminuria.

diuresis. Two months post partum, the blood pressure was 128 systolic and 80 diastolic and the urine contained albumin (1 plus). The patient had lost 40 pounds (18 Kg.) and had no complaints. Four months later the urine was free from protein. Two and one-half years after pregnancy, the blood pressure was 125 systolic and 75 diastolic but the urine contained albumin (2 plus). She was asymptomatic except for occasional edema of the ankles.

That a period of normalcy may exist between a toxemic pregnancy and the appearance of permanent recognizable vascular disease is unquestioned. Such factors as trauma of delivery, anesthesia and rest in bed undoubtedly mask the permanent vascular disease in some instances. The tendency of attributing hypertensive disease to a toxemic pregnancy that occurred many years before is common and often unjustifiable, since other causes of the hypertension may have arisen during the interim.

In the majority of cases of post-toxemic hypertension or albuminuria, blood pressure and urine never return to normal after delivery. The level of the blood pressure remains borderline or definitely elevated, and variable amounts of albumin persist in the urine. This early phase is illustrated in cases 5 to 8.

COURSE OF POST-TOXEMIC HYPERTENSION

In those persons in whom permanent vascular disease develops after toxemia of pregnancy the course is one of chronic progression, as in other types of hypertensive disease. At first the blood pressure may be borderline, normal on one occasion and somewhat elevated on another. In other cases it is definitely elevated on all occasions. Over a period of years it may gradually increase to high levels, or both systolic and diastolic pressures may suddenly rise from a moderate to a high level and take on the clinical aspects of malignant hypertension, as in case 5. In other instances, the course may be malignant from the start, as in case 7. We have been impressed by the rapid progression of the course of post-toxemic hypertension, the high levels to which both systolic and diastolic blood pressures may rise and the malignancy of the terminal phases of the disease.

Albuminuria may be the only indication of permanent residual renal impairment following toxemia (cases 4 and 8). This may persist in small or large degree for years unaccompanied by hypertension. The urinary sediment may contain many hyaline and granular casts and erythrocytes, resembling in every respect the urine of patients with chronic glomerulonephritis. We have not observed any instances of the so-called "nephrotic stage" of chronic glomerulonephritis in any of our cases of post-toxemic hypertension and albuminuria. Rapidly progressive hypertension may appear terminally (case 8), often in conjunction with renal failure, as in other types of chronic renal disease with albuminuria, such as chronic pyelonephritis and chronic glomerulonephritis.

At other times both hypertension and albuminuria are present throughout the postpartum course (cases 3 and 7). It is our impression that in those cases in which toxemia has been characterized mainly by hypertension during pregnancy the course post partum is predominantly hypertensive and that in those in which the toxemia is characterized primarily by albuminuria the course post partum is predominantly albuminuric.

Once established the post-toxemic hypertensive vascular disease resembles closely that of other types of vascular hypertension. For years there may be no symptoms whatsoever. Eventually, however, the brain, heart or kidneys succumb to the ravages of the disease, as in hypertensive disease of other causation. Such cerebral symptoms as headache, dizziness, nervousness, irritability, insomnia and paresthesia and eventually aphasia and hemiplegia may develop. The heart, at first normal, becomes enlarged, and symptoms and signs of cardiac insufficiency may appear. Finally, frank failure may ensue. Renal function, as determined by the urea clearance test, the concentration test and the phenolsulfonphthalein test may gradually and progressively diminish over the course of years. With the advent of frank renal insufficiency there is nitrogen retention in the blood.

Recent studies of renal clearance[7] have indicated that during toxemia of pregnancy the renal blood flow is essentially normal and the filtration rate some-

7. Chesley, L. C.; Connell, E. J.; Chesley, E. R.; Katz, J. D., and Glissen, C. S.: The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy, J. Clin. Investigation **19**:219 (Jan.) 1940. Chesley, L. C.: The Question of Glomerular Damage Following Toxemia of Pregnancy, Am. J. Obst. & Gynec. **42**:229 (Aug.) 1941. Corcoran, A. C., and Page, I. H.: Renal Function in Late Toxemia of Pregnancy, Am. J. M. Sc. **201**:385 (March) 1941. Taylor, H. C., Jr.; Wellen, I., and Welsh, C. A.: Renal Function Studies in Normal Pregnancy and in Toxemia Based on Clearances of Inulin, Phenol Red, and Diodrast, Am. J. Obst. & Gynec. **43**:567 (April) 1942. Welsh, C. A.; Wellen, I., and Taylor, H. C., Jr.: Renal Blood Flow, Filtration Rate, and Tubular Excretory Mass in Patients with Specific Toxemia of Pregnancy, J. Clin. Investigation **20**:438 (July) 1941. Wellen, I.; Welsh, C. A., and Taylor, H. C., Jr.:

(Footnote continued on next page)

what decreased. In those cases in which permanent postpartum hypertension develops, however, the clearances change after delivery in a manner indicating a decreased renal blood flow and an increased filtration rate, as in other types of chronic hypertensive disease. These observations contribute to the evidence that post-toxemic hypertension is similar to the chronic types of hypertensive disease, such as essential hypertension and chronic glomerulonephritis, and differs from the acute hypertension of toxemia.

In our experience, cases in which the course is primarily albuminuric are prone to terminate in renal insufficiency, whereas in those in which the course is predominantly hypertensive cardiac failure or cerebral hemorrhage develops terminally.

It is of value to follow a patient's course by periodic retinal examination. Vascular spasm, papilledema, retinal detachment, hemorrhages and exudates may appear during toxemia, but post partum they ordinarily disappear in the course

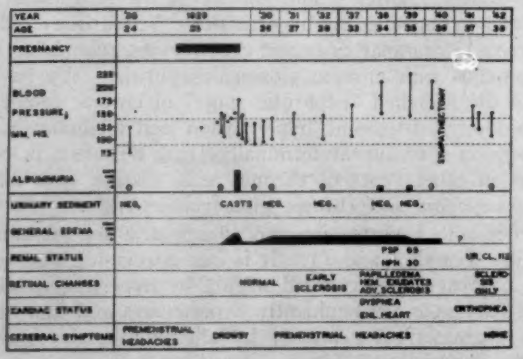

Fig. 5 (case 5).—Post-toxemic hypertension.

of weeks or months as the hypertension and albuminuria diminish.[1] During the ensuing years of post-toxemic hypertension the retinal vessels gradually become narrowed and their lumens irregular. The light reflex is increased, and arteriovenous "compression" becomes pronounced. The appearance of retinal hemorrhages and various types of exudate is usually an ominous sign. To date, we have not seen the classic albuminuric retinitis in the eyegrounds of any of our patients.

The following cases illustrate the salient features of post-toxemic hypertension.

Case 5 (fig. 5).—C. H. had had uncomplicated scarlet fever at the age of 2. Otherwise, the past history was noncontributory. Being a nurse, she was known to have had normal blood pressure (120 systolic and 75 diastolic) and urine before and after her marriage, in 1928. She became pregnant in 1929, at the age of 25. Blood pressures and results of urinalysis were normal through the twentieth week. At this time, the blood pressure rose to 148 systolic and 112 diastolic without albuminuria and she complained of morning headaches. Despite therapy the blood pressure remained elevated for the next nine weeks. During the twenty-ninth week she was found to have a blood pressure of 170 systolic and 106 diastolic and albumin (4 plus) in the urine, together with moderate generalized edema. After ten days of conservative therapy, the blood pressure remained the same, she became drowsy and labor was induced. A nonviable fetus was delivered. Post partum her blood pressure fell to 130 to 140 systolic and 90 to 100 diastolic for six months. Albuminuria disappeared, but she complained of intermittent edema.

The Filtration Rate, Effective Renal Blood Flow, Tubular Excretory Mass and Phenol Red Clearance in Specific Toxemia of Pregnancy, ibid. **21**:63 (Jan.) 1942. Dill, L. V.; Isenhour, M. A.; Cadden, M. A., and Schaffer, N. K.: Glomerular Filtration and Renal Blood Flow in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **43**:32 (Jan.) 1942.

From 1930 to 1937 the blood pressure remained at about 140 systolic and 110 diastolic with intermittent edema and no albuminuria. In 1937 the blood pressure rose rapidly to 175 to 240 systolic and 136 to 160 diastolic. The heart was found to be somewhat enlarged, and there was exertional dyspnea. Retinal hemorrhages and exudates and advanced changes in the vessels of the eyes appeared. The urine contained albumin (1 plus), but renal function as judged by the usual tests was normal. In 1941 sudden blindness associated with clouding of the sensorium occurred transiently. The patient complained of constant severe headache. A thoracolumbar sympathectomy was performed shortly thereafter by Dr. Reginald H. Smithwick, after which the blood pressure fell to about 155 systolic and 110 diastolic, the eyegrounds

Fig. 6 (case 5).—Biopsy section of renal tissue. Note the glomerular destruction, the arteriolar thickening and the relatively normal tubules. Phloxine-methylene blue stain; × 320.

improved, symptoms disappeared except for those associated with postural hypotension and renal function remained normal.

A biopsy of renal tissue (fig. 6) at the time of sympathectomy revealed advanced nephrosclerosis. The majority of the glomeruli were damaged, many being destroyed or hyalinized. Most of the tubules, on the other hand, appeared relatively normal in the biopsy section, although some showed minor degrees of atrophy. There was little increase in connective tissue elements. The arteriolar changes were striking and were characterized by muscular thickening of the media and narrowing of the lumens. These changes are those of nephrosclerosis.

Comment.—Normal prior to pregnancy, this patient experienced severe pre-eclampsia which lasted for ten weeks. Hypertension persisted post partum and became clinically malignant eight years after pregnancy, although it has been relieved at least temporarily by extensive sympathectomy.

CASE 6 (fig. 7).—B. N., a Negress, had a noncontributory familial and past history. There are no data available on her first four pregnancies. The fifth through the eighth pregnancy can be summarized as follows:

Pregnancy No.	Year	Highest Blood Pressure, Systolic/Diastolic	Albumin in Urine
5	1922	110/70	0
6	1925	Miscarriage	
7	1929	120/70	Rare +
8	1930	120/80	0

The ninth pregnancy occurred in 1932, when the patient was 38 years old, and was normal until the sixth month, when the blood pressure was 125 systolic and 80 diastolic and the urine did not contain albumin. Less than two weeks later she was admitted to the hospital because of three convulsions the day of entry. Her blood pressure was 222 systolic and 120 diastolic and the urine contained albumin (1 to 2 plus). After the administration of magnesium sulfate

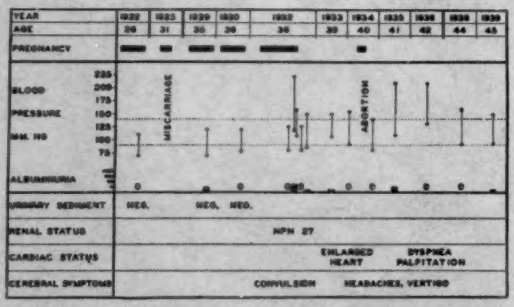

Fig. 7 (case 6).—Post-toxemic hypertension.

the blood pressure fell to 160 systolic and 110 diastolic. Five days later she was delivered spontaneously of a macerated fetus. Her postpartum course has been summarized as follows:

Year	Time Post Partum	Blood Pressure Systolic/Diastolic	Albumin In Urine	Symptoms
1932	7 days	150/100	+	0
	12 days	126/80	0	0
	1 mo.	150/86	±	Headaches
1933	1 yr.	150/106	±	Headaches; enlarged heart
1933	1½ yr.	156/90	0	Headaches; enlarged heart
1934	(Abortion and sterilization when patient 2½ months pregnant)			
1934	2 yr.	140/80	0	Headaches
1935	3 yr.	210/110	+	Headaches; vertigo; dyspnea; edema of the legs; palpitation
1936	4 yr.	210/130	0	Palpitation
1938	6 yr.	160/90	0	Headaches; dyspnea; vertigo
1939	7 yr.	150/90	±	Headaches; dyspnea; vertigo

Comment.—This is a rare example of permanent hypertension following an eclamptic pregnancy. The blood pressure and the urine had been normal during several earlier pregnancies. Convulsions occurred suddenly during the sixth month of the ninth pregnancy accompanied by severe hypertension and minimal edema. For at least seven years following eclampsia the patient had hypertension with cardiac and cerebral symptomatology but with albuminuria rarely.

CASE 7 (fig. 8).—M. L. O. had a noncontributory familial and past history. The first pregnancy occurred in 1935, when she was 18. There is no record of determination of blood pressure or examination of urine before or during the early months of pregnancy. She was admitted to the hospital during the eighth month with a blood pressure of 180 systolic and 140 diastolic and albumin (4 plus) in the urine. The sediment contained many white cells and an occasional cast. A stillborn infant was delivered shortly thereafter. After delivery the blood pressure remained elevated and albuminuria persisted, although she was symptom free.

In 1938 she delivered another stillborn infant. Shortly before delivery, the blood pressure was 224 systolic and 150 diastolic, and the urine contained albumin (4 plus). The sediment showed an occasional white blood cell and no casts. She was complaining of vomiting and blurring of vision. Examination revealed a detached retina. A third pregnancy terminated in a spontaneous abortion at three months. Vomiting had been the only symptom.

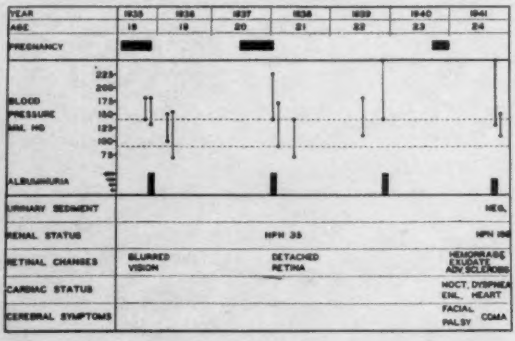

Fig. 8 (case 7).—Post-toxemic hypertension and albuminuria.

In 1941 she suffered a palsy of the left side of the face which persisted. Severe headaches and vomiting appeared. She was admitted to the hospital in severe cardiac decompensation. The blood pressure was 250 systolic and 130 diastolic; the urine contained albumin (3 plus), and the urinary sediment contained 10 to 15 red cells, occasional white cells and no casts. The blood level of nonprotein nitrogen was 186 mg. per hundred cubic centimeters. The patient died in uremia shortly thereafter.

At autopsy, the kidneys were small and contracted and the surface was granular. The capsule was thickened and adherent. The cortex was irregular and considerably thinner than normal. There was no evidence of pyelonephritis. Microscopically, the renal changes were those primarily of nephrosclerosis. The walls of the renal arterioles were greatly thickened, and narrowing of their lumens was pronounced, as may be seen in figure 9. Some glomeruli were intact, others obliterated and still others in various stages of destruction. Marked atrophy and destruction of tubular tissue were present with relatively few functioning units still intact. The destruction of glomeruli and tubules was reflected by a pronounced relative increase in the interstitial connective tissue.

The liver grossly and microscopically showed no abnormalities.

Comment.—The clinical history suggests that vascular disease was caused by toxemia of both the first and the second pregnancy. The course following the

second pregnancy was one of malignant vascular disease with death due to cardiac and renal insufficiency. Unfortunately, there is no record of blood pressure and urinalysis before the first pregnancy. Since autopsy showed nephrosclerosis and failed to reveal other causes for the vascular disease, it seems plausible to assume that it was caused by the toxemia of both the first and the second pregnancy.

Fig. 9 (case 7).—Section of kidney, showing advanced arteriolar thickening, glomerular and tubular destruction and interstitial fibrosis. Eosin–methylene blue stain; × 160.

Case 8 (fig. 10).—A. E. G. had a familial and past history which was of no significance. In 1922 results of a urinalysis were normal. During her first pregnancy, at the age of 25 in 1928, there were nausea and vomiting and generalized edema during the last trimester. At term, the blood pressure was 140 systolic and 86 diastolic and albumin (2 plus) was present in the urine, together with a few red cells and many hyaline and granular casts. In the latter half of the second pregnancy, in 1929, the blood pressure varied between 100 to 120 systolic and 70 to 80 diastolic throughout and the urine showed albumin (4 plus) on all occasions. There were

no toxemic symptoms. Labor was induced two weeks before term, and a normal infant was delivered. In 1932, between pregnancies, albumin (2 plus) was noted in the urine. In the same year there was an abortion at the third month of pregnancy, at which time the blood pressure was 120 systolic and 80 diastolic and the urine contained albumin (2 plus). During the fourth pregnancy, in 1935, albumin (4 plus) with occasional red cells and casts was noted in the urine at the eighth month and the blood pressure was 110 systolic and 80 diastolic. Delivery of a normal child occurred. From 1935 to 1940 the patient felt well and active. In 1940 fatigue, headaches, vomiting and blurred vision appeared. The blood pressure was found to be 215 systolic and 135 diastolic, the urine contained albumin (2 to 3 plus) and many red cells and casts; retinal vascular changes and hemorrhages were present, and frank cardiac failure and renal insufficiency (blood level of nonprotein nitrogen, 123 mg. per hundred cubic centimeters) were manifest. She went rapidly downhill and died of cardiac failure and uremia.

At autopsy both kidneys were contracted and presented a granular surface. The capsule was thickened, although not adherent. Several small cysts were present in the cortex of the left kidney. Microscopically, the renal architecture was markedly distorted, showing extensive areas of scarring and some areas of tubular hypertrophy and dilatation (fig. 11). All of the glomeruli were damaged, many being completely sclerosed and hyalinized. Many of the tubules were atrophic, while others showed evidence of regeneration. There was a diffuse increase in connective tissue elements. The arteriolar changes were striking. There was concentric

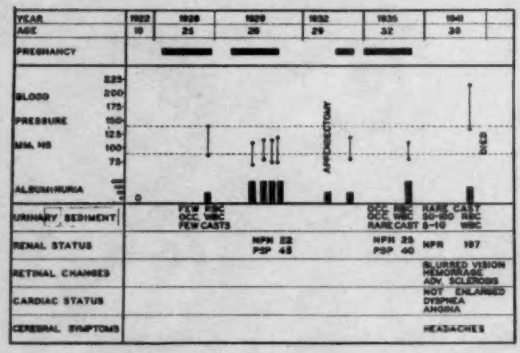

Fig. 10 (case 8).—Post-toxemic albuminuria.

thickening of the media with encroachment of the lumens. The larger vessels showed irregular hyaline intimal thickening and some medial fibrosis. No necrotizing lesions were seen.

No evidence of cirrhosis was found on histologic examination of the liver. Changes consistent with chronic passive congestion were the only abnormalities.

Comment.—After an albuminuric pregnancy in 1928 this patient's condition, previously normal, ran a course characterized mainly by albuminuria and terminal hypertension, with death due to uremia and cardiac failure.

The following case of post-toxemic hypertension is presented despite a lack of precise clinical data. In this case too, renal tissue for biopsy was taken at the time of sympathectomy.

Case 9.—E. M., aged 35, had nothing of significance in the familial and past history. Since the menarche she had had severe left-sided headaches with scintillating scotomas, nausea and vomiting premenstrually. The headaches became less severe and less frequent after marriage in 1929. During her first pregnancy, in 1931 at the age of 25, she had visited her physician monthly, starting at the second month. Blood pressure and urine were said to have been normal until the eighth month. During the seventh month massive edema of hands, feet and face appeared. One month before delivery hypertension and albuminuria were said to have appeared for the first time. She was treated medically and was delivered of a normal infant at term. The blood pressure remained elevated after this pregnancy, and small amounts of albumin were noted

in the urine on many occasions. Pregnancies occurred in 1933, 1935 and 1937. Two further pregnancies, in 1938 and 1940, were interrupted because of progressing hypertension. In 1942, the blood pressure was 230 systolic and 140 diastolic and the urine contained albumin (1 plus). The patient had complained of intense weakness for the two preceding years. She appeared worn and prematurely gray. Retinal examination showed only mild vascular change without

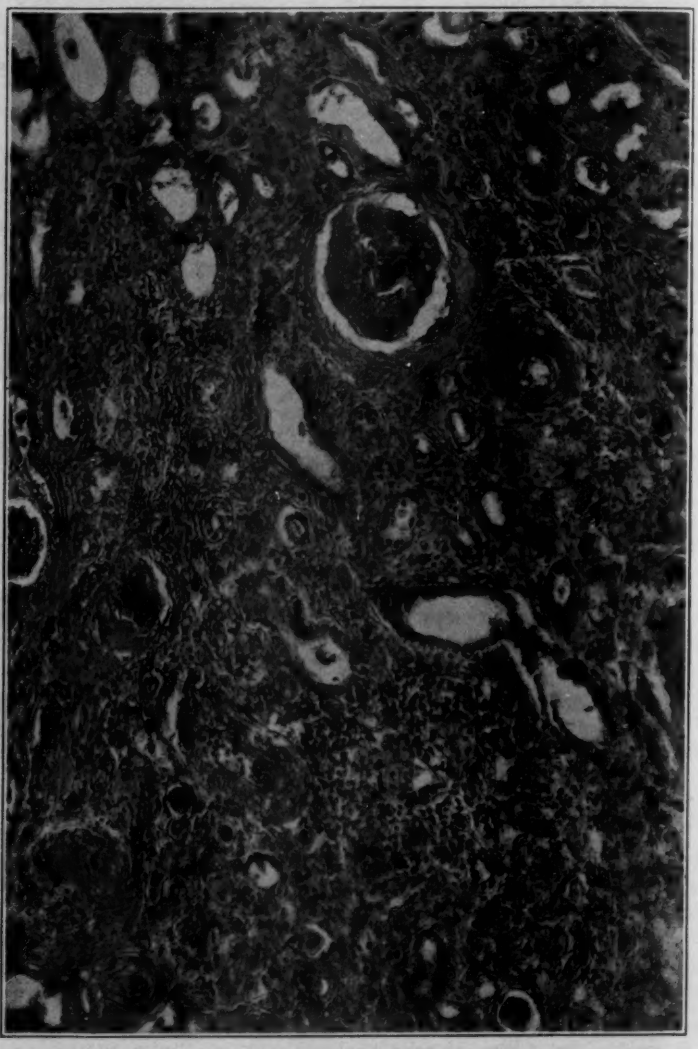

Fig. 11 (case 8).—Section of kidney, showing extensive scarring, damaged glomeruli and pronounced arteriolar changes. Eosin–methylene blue stain; × 160.

hemorrhage or exudate. Renal function was normal. In May 1942, the blood pressure was 275 systolic and 140 diastolic and the urine contained variable amounts of albumin (on one occasion the reaction for albumin was as great as 3 plus). A sympathectomy was performed in May 1942 by Dr. Reginald H. Smithwick, and renal tissue for biopsy was taken at the time of operation.

Renal Biopsy (fig. 12).—The renal arterioles showed sclerotic changes which, however, were not severe. The outstanding renal lesion microscopically was a diffuse degeneration of the tubular epithelium with swelling, degeneration, loss of contour and destruction. The glomeruli were only slightly damaged. Interstitial tissue was not increased.

COMMENT

Toxemia of pregnancy (preeclampsia and eclampsia) occurs in approximately 6 to 9 per cent of all pregnancies.[8] Furthermore, from examination of published reports it is apparent that roughly 25 per cent of women in whom toxemia develops are left with permanent postpartum vascular disease.[9] While these figures may be

Fig. 12 (case 9).—Biopsy section of renal tissue, showing diffuse degeneration of the tubular epithelium. Phloxine–methylene blue stain; × 320.

8. Stander, H. J.: An Analysis of Eight Hundred and One Cases of Toxemias of Pregnancy, New England J. Med. **201**:458 (Sept. 5) 1929. Dieckmann, W. J.: Renal Function in the Toxemias of Pregnancy, Am. J. Obst. & Gynec. **29**:472 (April) 1935. Page, E. W.: Relation Between Hydatid Moles, Relative Ischemia of the Gravid Uterus, and the Placental Origin of Eclampsia, ibid. **37**:291 (Feb.) 1939.

9. (*a*) Herrick, W. W., and Tillman, A. J. B.: Toxemia of Pregnancy: Its Relation to Cardiovascular and Renal Diseases; Clinical and Necropsy Observations with a Long Follow-Up, Arch. Int. Med. **55**:643 (April) 1935. (*b*) Dieckmann, W. J., and Brown, I.: Do Eclampsia and Pre-Eclampsia Cause Permanent Vascular Renal Pathology? Am. J. Obst. & Gynec. **37**:762 (May) 1939. (*c*) Reid and Teel.[5a] (*d*) Teel and Reid.[5]

high because of existing difficulties in the classification of cases derived from various sources, it will be noted, if one assumes their validity, that in 2 per cent of all women who become pregnant permanent hypertension develops after pregnancy.

The question has been raised as to whether toxemia has brought to light hitherto latent and unrecognized hypertension or whether it has actually been the factor initiating the vicious circle of permanent hypertensive disease. We believe the latter to be true in the light of the known facts both of clinical and of experimental hypertension.

Toxemia of pregnancy is a well defined disease entity. It is an acute type of vascular disease occurring during the last half of pregnancy, usually accompanied by greater or lesser degrees of water retention, sometimes subsiding before delivery and always after delivery. It may appear in women with hitherto normal blood pressure, as well as in those who are already hypertensive.

Its closest analog in a nonpregnant person is acute glomerulonephritis, from which it differs clinically mainly by the absence of preceding infection of the respiratory tract and lack of erythrocytes in the urinary sediment in all but the most severe cases. Just as acute glomerulonephritis differs clinically and pathogenetically from the chronic type of hypertension following it or from the hypertension appearing in association with pyelonephritis, endocrinopathies, arteritides, congenital anomalies or from the idiopathic type ("essential" hypertension), so does the vascular disorder of toxemia of pregnancy differ. There is no evidence warranting the postulation of previous latent hypertension in patients in whom acute glomerulonephritis and subsequent hypertension develop. Similarly, there is no good evidence for its existence in those in whom permanent hypertension develops after toxemia. Both diseases represent acute hypertension of short duration which may subside rapidly leaving no after-effects, may leave sequelae taking months to heal or may leave a permanent vascular disease which is to be clearly distinguished from the acute process which produced it and which in the meantime has subsided.

Isenhour and his co-workers [10] have recently studied average blood pressure and incidence of hypertension in a group of 900 parous and 900 nulliparous women subdivided into 10 year age groups. They found no increase in either the average blood pressure or the incidence of hypertension among the parous women, regardless of age group. The authors concluded that toxemia of pregnancy is not an etiologic factor in hypertension nor does it hasten its appearance in women predisposed to this disease. This conclusion does not seem warranted on the basis of a series which when subdivided into decades is so small. This is particularly evident in the younger age groups (20 to 29 and 30 to 39), in which the gross incidence of hypertension was comparatively low (about 2 and 5 per cent). If toxemia of pregnancy were responsible for 10 per cent of the instances of hypertension in these age groups, a much larger series than that reported would be required to show a significant increased incidence of hypertension due to this cause.

It is perhaps important to emphasize the obvious fact that chronic hypertensive disease is in itself a disease entity which after a certain stage is irreversible, even if the initiating lesion is removed, be it a unilateral pyelonephritic kidney or toxemia of pregnancy. The chronic forms of hypertensive vascular disease all behave similarly, as is indicated by the universal difficulty of differentiating the various causations on clinical and even on pathologic grounds. The brain, the heart and the kidneys are the organs most affected, and their eventual failure is the cause of death in the great majority of cases. The course of the chronic disease is flavored

10. Isenhour, C. E.; Kuder, K., and Dill, L. V.: The Effect of Parity on the Average Blood Pressure and on the Incidence of Hypertension, Am. J. M. Sc. **203**:333 (March) 1942.

somewhat by the initiating lesion. Thus in cases of so-called "essential" hypertension death occurs usually as a result of cerebral hemorrhage or cardiac failure. In cases of chronic glomerulonephritis, on the other hand, the majority of deaths are due to renal insufficiency. The course of post-toxemic hypertension may simulate that of chronic glomerulonephritis or that of benign or malignant "essential" hypertension. Death may result from cerebral hemorrhage, cardiac failure or uremia, particularly the last.

Heynemann [11] studied pathologically the kidneys of 7 patients dying years after eclamptic pregnancies and observed nephrosclerosis in 6 and chronic pyelonephritis in 1. Herrick and Tillman [9a] described 11 cases of toxemia of pregnancy in which autopsy was done; on histologic examination they encountered nephrosclerosis in 7 cases and chronic glomerulonephritis in 4 cases. Bell [12] stated that he considered the pathologic change in toxemia to be a special form of glomerulonephritis, at least partially inflammatory in nature, and expressed the opinion that he could recognize characteristic lesions in the kidneys of a patient dying seven years after eclampsia. This work has not been confirmed, however, and Page and Cox [13] failed to find any specific pathologic condition post partum. The only constant change was a nonspecific thickening of the basement membrane of the glomerular capillaries. Thus, the observations of these various authors indicate that the kidneys of patients dying of hypertensive vascular disease which originated years earlier in a toxemic pregnancy have the histologic changes characteristic of chronic vascular nephritis (nephrosclerosis) or of chronic glomerulonephritis but not of preeclampsia or eclampsia. From our own data we are in accord with these observations and interpretations.

Histologic examination of the kidneys of our patients revealed nephrosclerosis as the basic and characteristic lesion. The characteristic renal changes of toxemia, the glomerulonephrosis of Fahr,[14] were absent. This indicates that the specific lesions of toxemia had "healed."

It is apparent that the kidneys may show a varied pathologic picture years after toxemia of pregnancy. Arteriolar change, consistent with hypertensive vascular disease, was seen in all our cases and in those reported by other investigators. The pathologic change may be limited to this lesion or may include varying degrees of glomerular scarring and tubular degeneration. It is frequently impossible to distinguish post-toxemic kidneys from those of chronic glomerulonephritis. This is not surprising, for the acute stages of both diseases are characterized by a diffuse glomerular lesion, inflammatory in the case of glomerulonephritis, degenerative in the case of toxemia. Just as the lesions of acute glomerulonephritis are not to be found in the kidneys of patients dying years later of chronic glomerulonephritis, so also glomerulonephrosis of Fahr,[14] characteristic of toxemia, is not encountered in the kidneys of persons dying years later of chronic vascular disease. This pathologic relation is of more than casual interest in view of the frequent similarity of both the acute and the chronic clinical syndrome. It is a common observation that the chronic effects of various types of initial renal lesions are identical or at least similar. In our cases, as well as in those reported by other investigators,

11. Heynemann, T.: Spätfolgen der Eklampsie und ihrer Vorstadien unter besonderer Berücksichtigung der Nierenveränderungen, Zentralbl. f. Gynäk. **58**:3010 (Dec. 22) 1934.

12. Bell, E. T.: Renal Lesions in the Toxemias of Pregnancy, Am. J. Path. **8**:1 (Jan.) 1932.

13. Page, E. W., and Cox, A. J.: Renal Changes Following Toxemias of Late Pregnaney, West. J. Surg. **46**:463 (Sept.) 1938.

14. Fahr, T.: Die pathologisch-anatomischen Veränderungen der Niere und Leber bei der Eklampsie, in Hinselmann, H.: Die Eklampsie, Bonn, Friedrich Cohen, 1924.

the kidneys revealed changes practically identical with those in kidneys of patients dying of chronic glomerulonephritis and of "essential" hypertension.

No evidence of cirrhosis of the liver was observed in our 2 cases in which autopsy was done.

The importance of recognizing this group of patients with post-toxemic hypertension lies not so much in its treatment as in its prevention. In the great majority of cases this disease is preventable by interrupting pregnancy before the hypertension or albuminuria of toxemia has lasted for more than three weeks. This applies as much to mild as to severe toxemia. Furthermore, Irving [15] has demonstrated that the fetus, if anything, benefits by delivery occurring between the thirty-second and the thirty-sixth week of pregnancy rather than later. This is the commonest time of appearance of toxemia of pregnancy.[1]

SUMMARY

The rather common occurrence of permanent vascular disease following toxemia of pregnancy (preeclampsia and to a less extent eclampsia) is described and the clinical course of this hypertension studied.

The clinical analogy between toxemia of pregnancy and acute glomerulonephritis as regards the acute phases and the late effects on the vascular system is pointed out.

The duration, more than the severity, of the toxemia during pregnancy determines the development of permanent postpartum vascular disease.

A latent period of at least several months may intervene between toxemia of pregnancy and the development of recognizable permanent hypertension or albuminuria.

After toxemia of pregnancy hypertension may persist for at least a year and then disappear.

The postpartum course may be predominantly hypertensive or albuminuric, apparently dependent on a similar predominance in pregnancy.

The course is prone to be rapidly progressive in comparison with that of other types of hypertension.

Death usually occurs as a result of uremia, cardiac failure or cerebral hemorrhage, as in other types of hypertension. Retinal changes, such as vascular sclerosis, hemorrhages and exudates, occur, but no instances of true albuminuric retinitis have been observed.

Nephrosclerosis is the characteristic postmortem finding. The pathologic condition in the kidneys in other respects is variable, however, and at times may duplicate that of chronic glomerulonephritis. This is not surprising, as both diseases start with a diffuse glomerular lesion and the hypertensive vascular disorders following the two diseases may run almost identical clinical courses.

The importance of recognizing this group of patients with post-toxemic hypertension lies in its prevention. The late vascular effects of toxemia may be prevented by interrupting pregnancy before the hypertension and albuminuria of toxemia have lasted for more than three weeks. This applies as much to mild as to severe toxemia.

Dr. A. J. B. Tillman gave us permission to cite several cases from the records of the Sloane Hospital for Women, and Dr. Reginald H. Smithwick and Dr. Benjamin Castleman allowed us to examine the clinical and pathologic material in the 2 cases in which biopsy of renal tissue was done. Dr. Orville Bailey aided us in the interpretation of the pathologic material and photographed the microscopic sections presented.

Peter Bent Brigham Hospital.

15. Irving, F. C.: A Study of Consecutive Cases of Hypertension and Albuminuria in Pregnancy, Pennsylvania M. J. **44**:557 (Feb.) 1941.

FRIEDLÄNDER'S BACILLUS SEPTICEMIA AND MENINGITIS

REPORT OF A CASE AND AUTOPSY, WITH AN ANALYSIS OF TWENTY-NINE CASES COLLECTED FROM THE LITERATURE

JOHN C. RANSMEIER, M.D.
AND
JAMES W. MAJOR, M.D.
NASHVILLE, TENN.

Meningitis caused by Friedländer's bacillus is a medical rarity. The case to be reported is of interest because of the scarcity with which reports of this disease have appeared in the American literature. It serves also to illustrate the danger of confusion with meningococcic meningitis. Until recently Friedländer's bacillus meningitis was almost uniformly fatal, but in the last two years some cures have been obtained with sulfapyridine[1] (2-[paraaminobenzenesulfonamido]-pyridine) as well as with sulfadiazine[2] (2-[paraaminobenzenesulfonamido]-pyrimidine), which has become available subsequent to the occurrence of our case. It is hoped that in the future early diagnosis and vigorous use of the proper drug may make successful treatment more generally possible. Since it appears that the dawn of a new era in the therapy of this formidable disease is being witnessed, a consideration of 29 cases collected from the available literature is included as a background against which present developments may be evaluated.

REPORT OF CASE

History.—E. B. J., a 73 year old white man, was brought to the hospital on Oct. 30, 1940 in stupor. After a two year history of urinary symptoms culminating in complete retention he had entered another hospital six weeks previously. Treated with retention catheter, he improved and was discharged on October 24. At home he had no significant complaints until October 29, when he began to suffer from progressive headache, backache and malaise, followed by a shaking chill and fever, with a temperature of 103 F. On October 30 he became gradually less responsive and was admitted to the surgical service of Vanderbilt University Hospital.

Physical Examination.—His temperature was 102 F. (rectal), pulse rate 104, respiratory rate 24 and blood pressure 110 systolic and 70 diastolic. The patient was acutely ill and semiconscious. The pupils reacted normally, and there was no papilledema. The nose and ears were not remarkable. Moderate injection of the pharynx was observed. Most of the teeth were absent, and the remainder were extremely carious. Some increased resistance to flexion of the neck was noted, but true rigidity was not observed. Kernig's sign was absent. The heart did not seem enlarged on percussion, the rhythm was regular and no murmurs were heard. A few rales were detected at the bases of the lungs. The abdomen presented slight resistance without true muscle spasm. There was some tenderness in the right flank and costovertebral angle. The prostate was enlarged, irregular and firm. Several hard

From the Department of Medicine and the Department of Pathology, Vanderbilt University School of Medicine.

1. (*a*) Robertson, C. W.: Meningitis Due to B. Friedländeri: Recovery of a Case Treated with Sulfapyridine, Canad. M. A. J. **45**:70 (July) 1941. (*b*) Montes, G. G., and Real, W. A.: Meningitis purulenta a neumobacilo de Friedländer (Klebsiella pneumoniae) curado con dagenan, Bol. Soc. cubana de pediat. **12**:5 (Jan.) 1940.

2. (*a*) Julianelle, L. A.: Personal communication to the authors. (*b*) Trevett, G. I.; Nelson, R. A., and Long, P. H.: The Clinical Use of Sulfadiazine in the Therapy of Bacterial Infections Other than Pneumonia, Bull. Johns Hopkins Hosp. **69**:303 (Oct.) 1941.

nodules were noted in it and in the right seminal vesicle. The tendon reflexes were physiologic, the plantar response was flexor on both sides and clonus was absent.

Course in Hospital.—The blood on admission contained 5,600,000 red cells and 22,000 leukocytes per cubic millimeter, 86 per cent of the latter being polymorphonuclear leukocytes, 10 per cent lymphocytes and 4 per cent monocytes. The hemoglobin measured 14 Gm. per hundred cubic centimeters. The Kahn reaction of the blood was negative. Catheterization yielded 200 cc. of cloudy urine containing 200 to 300 leukocytes and 3 or 4 erythrocytes per high power field in the centrifuged sediment. A trace of albumin was present, but there was no reduction with Benedict's solution. A retention catheter was inserted, and later specimens of urine revealed diminishing numbers of pus cells. The nonprotein nitrogen content of the blood was 50 mg. per hundred cubic centimeters on admission but rose to 57 mg. on the second hospital day despite the parenteral administration of fluids. On October 31 the patient sank into a coma, his neck became stiff and a lumbar puncture was done. The spinal fluid was purulent, was under an initial pressure of 150 mm. and contained 2,800 cells, almost all of which were polymorphonuclear leukocytes. The reaction to Pandy's test was positive, and a pellicle formed when the fluid stood. No organisms were found in smears.

The patient was then transferred to the medical service. Examination revealed coma and rapid respirations with irregularly recurring intervals of apnea. The skin was sprinkled with petechiae varying from bright rose to dusky brown and from 1 to 3 mm. in diameter, being most numerous on the chest but occurring also on the abdomen and extremities and in the palpebral conjunctiva of each eye. The neck was very stiff and Kernig's sign absent. A sustained ankle clonus and a questionable extensor plantar response were present on the left.

A hard shaking chill occurred. On the supposition that the patient was suffering from meningococcic meningitis, 6 Gm. of sulfanilamide was administered by hypodermoclysis, and a Levine tube was inserted into the stomach, through which an additional 5 Gm. was given, followed by 2.1 Gm. every four hours with equal amounts of sodium bicarbonate. Lumbar puncture was repeated on the morning of November 1, with removal of 30 cc. of turbid fluid containing 5,510 cells per cubic millimeter, of which 96 per cent were polymorphonuclear leukocytes. No definite organisms were found in Gram strains of the sediment after centrifugation. The level of free sulfanilamide in the blood and spinal fluid at that time were 20.2 and 15.1 mg. per hundred cubic centimeters, respectively. The dose of the drug was reduced to 1.2 Gm. and later in the day to 0.9 Gm., with equal amounts of sodium bicarbonate, given every four hours by Levine tube, and administration was continued at the latter dosage until the patient's death.

Toward evening lumbar puncture was repeated, with similar results. No organisms could be seen on careful search and cultures had not as yet shown growth. This strengthened the impression of meningococcic infection, and the patient was given intravenously 60,000 units of meningococcus antitoxin (Parke, Davis & Company) diluted with 10 per cent dextrose solution. Later the pulse became very rapid and an electrocardiogram showed auricular flutter. Fever persisted, the temperature reaching as high as 105.4 F. (fig. 1). Death occurred on the morning of November 2, early in the fifth day of illness and about sixty-eight hours after admission to the hospital.

Bacteriologic Observations.—Spinal fluid obtained on October 31 yielded no growth on blood agar, on cooked chocolate agar slants or in dextrose infusion and sodium thioglycollate broths. Two specimens of spinal fluid taken on November 1 showed Friedländer's bacillus in all these mediums. Cultures of urine taken on October 31 and November 1 showed pure growth of the same organism, which was also shown by the patient's blood drawn October 31 before institution of sulfanilamide therapy but only in dextrose broth after thirty-six hours' incubation.

Study of the organism showed it to be a nonmotile, pleomorphic, gram-negative encapsulated bacillus with rounded ends and a tendency to bipolar staining. On blood agar the colonies were round, white, lustrous, opaque, mucoid and characteristically stringy when touched with the loop. Growth was luxuriant and confluent in subcultures on solid mediums, including plain beef infusion agar. There was no hemolysis of blood agar or blood broth. Abundant growth occurred in sodium thioglycollate broth,[3] demonstrating facultative anaerobiasis. Lactose, dextrose, xylose, mannitol, maltose and sucrose were readily fermented, with production of acid and gas. Tests for indole formation gave negative results. A white mouse

3. Brewer, J. H.: Clear Liquid Mediums for the "Aerobic" Cultivation of Anaerobes, J. A. M. A. **115**:598 (Aug. 24) 1940.

was inoculated intraperitoneally with 0.25 cc. of a twenty-four hour broth culture and died in less than eighteen hours. The same organism was recovered in large numbers from its heart's blood and stringy peritoneal exudate. Neither a *Quellung* reaction nor agglutination could be demonstrated in antipneumococcus type II serum. A subculture from the patient's spinal fluid was sent to Dr. Louis A. Julianelle, and he confirmed the identification of the organism as Friedländer's bacillus and classified it as serologic type B.

Autopsy.—The body was somewhat emaciated. Petechiae were present over the body generally and in the conjunctival sacs. Moderate amounts of clear serous fluid were present in the peritoneal and pleural cavities. The pericardial sac was normal. The heart weighed 450 Gm., and a few small white opaque areas measuring 1 to 2 mm. in diameter were present in the epicardium. Section revealed the same kind of lesions scattered throughout a thickened myocardium. The lungs showed only emphysema, but the bronchial mucosa con-

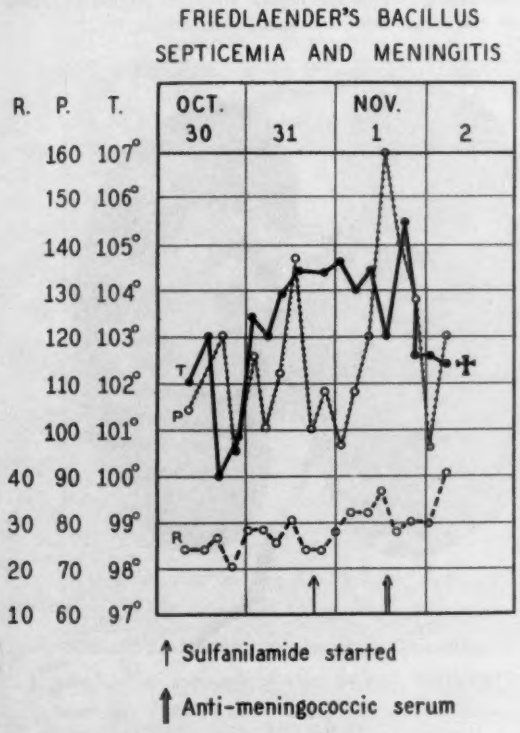

Fig. 1.—Record of respiratory rate, pulse rate and temperature in a case of Friedländer's bacillus septicemia and meningitis.

tained many petechiae and was covered by a gelatinous purulent exudate. The serosa of about 4 feet (122 cm.) of the midportion of the small intestine presented many hemorrhagic areas measuring 0.5 to 1 cm. in diameter. The corresponding intestinal mucosa was riddled with shallow, soft hemorrhagic ulcers varying from 2 to 5 mm. in diameter. The liver weighed 1,950 Gm. and contained many small irregular yellowish opaque areas scattered over its surface and throughout its substance. These measured 2 to 5 mm. in diameter. The spleen, pancreas and adrenals were not remarkable. The kidneys were enlarged, weighing 250 to 300 Gm. Their capsules were partially adherent, and both on the surface and throughout the kidney substance on section many small yellowish opaque lesions of the same type were seen (fig. 2). There was no evidence of mucosal inflammation in the genitourinary tract. The

prostate was firm and irregular. After removal of the brain the meninges presented a slight diffuse haziness but no definite exudate. The vessels and nerves were normal, and the lateral sinuses were uninvolved.

Microscopic examination revealed the minute lesions of the myocardium, liver and kidneys to be miliary abscesses, some of which were also found in the pancreas and adrenals. They were composed of centers of necrotic material containing polymorphonuclear cells and fibrin surrounded by an acute exudate with some fibroblastic proliferation. An acute bronchitis was present but no notable pneumonitis. The intestinal ulcers presented an acute inflammatory appearance and were superficial, not involving the muscular layers. The kidney pelves showed no inflammation. Carcinoma of the prostate was present. Sections of the brain revealed a diffuse acute purulent leptomeningitis with polymorphonuclear leukocytes predominating in the exudate. Some vessels within the brain were surrounded by groups of polymorphonuclear cells.

Cultures of the blood, meninges, bronchi and hepatic abscesses yielded an organism identical with the one isolated from the blood, urine and spinal fluid during life.

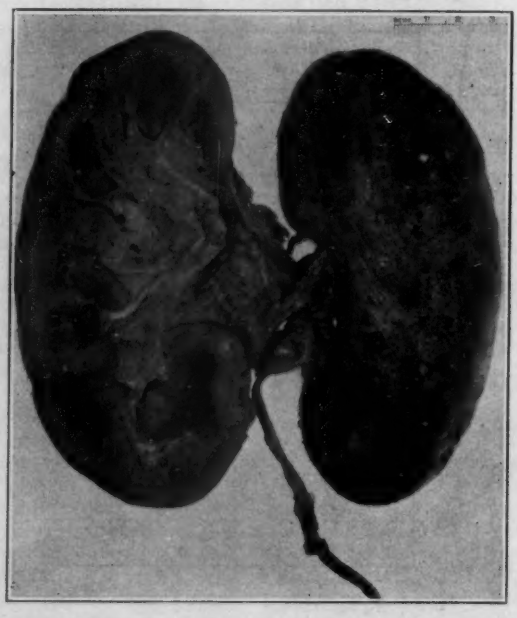

Fig. 2.—Photograph showing embolic abscesses in the kidney.

COMMENT

The portal by which the infection gained entry cannot be stated with certainty. Since the lesions observed in the urinary tract at autopsy appeared to be hematogenous, it was felt unlikely that the infection began there. Although the existence of a purulent bronchitis suggested the possibility of origin in the respiratory system, the history failed to substantiate this theory. In view of the extensive and rather unusual ulcerative lesions in the small intestine, it may be that the infection began as enteritis, with invasion of the blood stream resulting in embolic abscesses throughout the viscera and terminal meningitis. Banti [4] reported a fatal case of Friedländer's bacillus septicemia, likewise without diarrhea, in which similar ulcerations were seen involving the colon and ileum.

4. Banti, G.: Sopra quattro nuove specie di protei o bacilli capsulati, Sperimentale **62**:139 (Aug.) 1888.

ANALYSIS OF THIRTY CASES OF FRIEDLÄNDER'S BACILLUS MENINGITIS

Meningitis due to Friedländer's bacillus is uncommon in the United States. Etiologic analysis of several large series of cases from various cities revealed that the meningitis was caused by Friedländer's bacillus in only 3 of a total of 3,714 cases. The case of Fothergill and Sweet [5e] is, to our knowledge, the only one of these which has been reported. Single instances of Friedländer's bacillus meningitis in this country have been described by Rothschild,[6] Gowen [7] and Kolmer and Rule.[8] In addition, Robertson has reported a case from Canada [14a] and Montes and Real [14b] 1 from Cuba. Most of the publications concerning this disease have appeared in European journals. The first case was recorded by Weichselbaum [9] (cited by Etienne [10]) only six years after Friedländer's original description of the organism, in 1882.

We have been able to collect data on 30 cases of meningitis caused by encapsulated bacilli of the Friedländer group, consisting of our own and 29 cases from the available literature, as listed in table 1. Since it appears from the work of Julianelle,[11] Edwards [12] and Osterman and Rettger [13] that Friedländer's bacillus and Bacterium aerogenes are closely related, if not indistinguishable, a few cases in which the disease was attributed to the latter organism are included.[14]

Sex, Race and Age.—Of the 30 patients reported on, 19 were males and 8 females, and for 3 the sex was not stated. One patient was a Negro,[6] 2 were Chinese [14c] and the remainder were presumably of the white race. The age distribution is shown in table 2. On the basis of the age incidence observed by Neal in 1,496 cases of nontuberculous meningitis of all causes,[5d] the expected number for

5. (*a*) Holt, L. E.: Observations on Three Hundred Cases of Acute Meningitis in Infants and Young Children, Am. J. Dis. Child. **1**:26 (Jan.) 1911. (*b*) Dunn, C. H.: Cerebrospinal Meningitis: Its Etiology, Diagnosis, Prognosis and Treatment, ibid. **1**:95 (Feb.) 1911. (*c*) Gilbert, R., and Coleman, M. B.: Incidence of Various Species of Bacteria in Spinal Fluids from Cases of Meningitis, J. Lab. & Clin. Med. **13**:547 (Feb.) 1928. (*d*) Neal, J. B.: Experience of the Meningitis Division of the New York Department of Health, Am. J. Pub. Health **21**:147 (Feb.) 1931. (*e*) Fothergill, L. D., and Sweet, L. K.: Meningitis in Infants and Children with Special Reference to Age Incidence and Bacteriological Diagnosis, J. Pediat. **2**:696 (June) 1933.

6. Rothschild, K.: Meningitis Caused by Friedländer's Bacillus, J. A. M. A. **97**:1956 (Dec. 26) 1931.

7. Gowen, G. H.: A Case of Friedländer's Bacillus Meningitis Secondary to Bilateral Otitis Media, Illinois M. J. **65**:533 (June) 1934.

8. Kolmer, J. A., and Rule, A. M.: Sulfanilamide and Sulfapyridine in Treatment of B. Friedländer (Klebsiella Pneumoniae) Infections of Mice, Proc. Soc. Exper. Biol. & Med. **42**:305 (Oct.) 1939.

9. Weichselbaum, A.: Ueber eine von einer Otitis media suppurativa ausgehende und durch den Bac. pneumoniae (Friedländer) bedingte Allgemeininfektion, Monatschr. f. Ohrenh. **22**:200 and 229 (Aug.) 1888.

10. Etienne, G.: Le pneumobacille de Friedländer: Son rôle en pathologie, Arch. de méd. expér. et d'anat. path. **7**:124, 1895.

11. Julianelle, L. A.: Immunological Specificity of Bact. Aerogenes and Its Antigenic Relation to Pneumococcus Type II and Friedländer's Bacillus Type B, J. Immunol. **32**:21 (Jan.) 1937.

12. Edwards, P. R.: Relationships of the Encapsulated Bacilli with Special Reference to Bact. Aerogenes, J. Bact. **17**:339 (May) 1929.

13. Osterman, E., and Rettger, L. F.: A Comparative Study of Organisms of the Friedländer and Coli-Aerogenes Groups, J. Bact. **42**:699 (Dec.) 1941.

14. (*a*) Beitzke, H.: Ueber einen Fall von Meningitis, verursacht durch Bacterium lactis aërogenes, Centralbl. f. Bakt. (Abt. 1) **37**:496, 1904. (*b*) Deane, A., and Shera, G.: A Case of Infection of the Meninges by Bacillus Lactis Aerogenes, Lancet **2**:1237 (Dec. 15) 1928. (*c*) Davis, L. J., and Fernando, F. S.: Meningitis Due to Mucoid-Encapsulated Bacilli [case 1], Tr. Roy. Soc. Trop. Med. & Hyg. **29**:143 (July) 1935.

each of the three large age groups shown has been calculated and compared with that observed. Below the age of 3 years the incidence was about what might be expected. It should be mentioned that a large proportion of these patients (9 out of 11) were under 9 months of age. The age group from 3 to 20 years was

TABLE 1.—*Thirty Cases of Friedländer's Bacillus Meningitis*

Published by	Year Published	Patient's Sex	Patient's Age	Probable Primary Focus	Other Extrameningeal Foci	Outcome
Weichselbaum [9]	1888	F	54 yr.	Otitis media	Mastoiditis, eustachian salpingitis, paranasal sinusitis	Death
Dmochowski [13a]	1894	M	54 yr.	Sphenoid and maxillary sinusitis	Osteomyelitis of facial bones, phlegmon of face, brain abscess	Death
Etienne [10]	1895	M	33 yr.	Pneumonia	Empyema, arthritis	Death, 6 days
Brunner [11]	1896	M	55 yr.	Otitis	Petrositis, sinus thrombosis, embolic abscesses in kidneys	Death, 6 weeks
Jassniger [16]	1901	M	16 yr.	Sphenoid sinusitis	Cavernous sinus phlebitis	Death, 7 days
Beitzke [14a]	1904	M	3 wk.	Unknown	None found	Death, 18 days
Bonhoff and Esch [22a]	1912	..	Newborn	Otitis	.....	Death, 14 days
Siredey, Lemaire and de Jong [18]	1912	M	26 yr.	Pharyngitis	None found	Death, 12 days
Rénon and Blamoutier [19]	1921	F	44 yr.	Otitis	Petrositis	Death
Elias, [24a] case 1	1924	M	62 days	Bronchitis ?	Paravertebral pneumonia	Death
Menetrier and Bertrand-Fontaine [20]	1924	M	33 yr.	Unknown	None found	Death, 4 days
Lion and Minvielle [24b]	1924	M	38 yr.	Pneumonia	Abscess of lung	Death, 23 days
Dufourt, Delattre and Bonnet [17]	1926	..	9 mo.	Arthritis, ankle and elbow	None found	Death, 2½ mo.
Papandrea, [23] case 1	1927	F	5 mo.	Pneumonia	Pleuritis, pericarditis	Death, 26 days
Papandrea, [23] case 2	1927	M	2½ yr.	Unknown	None found	Death, 5 days
Brain and Valentine [25a]	1928	M	22 yr.	Otitis	Mastoiditis (postoperative)	Death, 22 days
Deane and Shera [14b]	1928	F	71 yr.	Cholecystitis	None found	Death, 9 days
Rothschild [6]	1931	M	34 yr.	Otitis	Mastoiditis, subdural abscess	Recovery
Comte, Lévy-Bruhl and Dany [25]	1931	M	50 yr.	Unknown	None found	Death, 7 days
Fotbergill and Sweet [5a]	1933	M	4 wk.	Unknown	None found	Death
Gowen [7]	1934	F	63 yr.	Otitis	Mastoiditis, abscesses in neck and arm	Death, 3 mo.
Davis and Fernando, [14c] case 1	1935	F	29 yr.	Uterine infection ?	None found	Death, 9 days
Davis and Fernando, [14c] case 2	1935	M	1 mo.	Unknown	Basal pneumonia (? terminal)	Death, 11 days
Leenhardt, Boucomont and Balmès [24c]	1937	..	4½ mo.	Unknown	None found	Death, 8 days
Sicard and Pluvinage [25b]	1937	F	58 yr.	Frontal sinusitis	Osteomyelitis frontal bone	Death, 4 weeks
Kolmer and Rule [5]	1939	M	36 yr.	Frontal, ethmoid and sphenoid sinusitis	None found	Death, 11 days
Sloboziann and Ionescu [23b]	1940	F	Newborn	Pneumonia	None found	Death, 4 days
Montes and Real [15]	1940	M	2 yr.	Unknown	None found	Recovery
Robertson [1a]	1941	M	49 yr.	Maxillary sinusitis	? Bronchopneumonia	Recovery
Ransmeier and Major	1942	M	73 yr.	Unknown	Bronchitis, enteritis, miliary abscesses in viscera	Death, 5 days

surprisingly spared (14 patients expected, 1 observed), while a preponderance of the patients were adults (5 expected, 18 observed), many of them in the later decades of life. From this series it appears that Friedländer's bacillus meningitis, like other varieties, may occur in infants but is peculiar in that it tends to spare children over 3 years of age and has an unusual predilection for older adults.

Probable Primary Focus.—The portal of entry for the infection is of the greatest interest but cannot always be established. The probable primary foci in 30 cases

are shown in tables 1 and 3. It will be noted that infections of the middle ear, mastoid and sinuses were found in over half the adults, while in the majority of the patients under 3 years of age the primary focus was unknown. Chronic disease of the ear and sinus of many years' duration may provide the avenue for invasion of the meninges in adults, while the sinuses are poorly developed in infancy and would not be expected to be of importance in that period of life. In 2 of the adults extremely severe sinusitis with osteomyelitis of the bony walls of the frontal and maxillary sinuses was observed,[15] while in 1 case the cavernous sinus was involved secondarily to sphenoid sinusitis.[16] Pneumonia was considered a precursor of Friedländer's bacillus meningitis in only 5 cases. Single cases in which the disease was probably secondary to cholecystitis,[14b] arthritis [17] and uterine infection

TABLE 2.—*Comparison of Age Incidence in 30 Cases of Friedländer's Bacillus Meningitis with that Observed in 1,496 Cases of Nontuberculous Meningitis of All Causes*

Age Group	Cases of Nontuberculous Meningitis (Neal [84])		Friedländer's Bacillus Meningitis, Number of Cases	
	Number	Per Cent	Observed	Expected
Under 3 years	509	34	11	10.2
3 to 20 years	716	48	1	14.4
Over 20 years	271	18	18	5.4
Total	1,496	100	30	30.0

TABLE 3.—*Probable Primary Focus in 30 Cases of Friedländer's Bacillus Meningitis, According to Age* *

Probable Primary Focus	Number of Cases in Age Groups		
	Under 3 Years	16 to 73 Years	Total
Otitis, mastoiditis, etc.	1	6	7
Paranasal sinusitis	..	5	5
Pneumonia, bronchitis	3	2	5
Pharyngitis	..	1	1
Cholecystitis	..	1	1
Arthritis	1	..	1
Uterine infection ?	..	1	1
Unknown	6	3	9
Total	11	19	30

* None of the patients were between 3 and 16 years of age.

(Davis and Fernando,[14c] case 1) have been reported. Pharyngitis was thought to have been the primary focus in 1 instance.[18] Since it is known that Friedländer's bacillus may occasionally be isolated from the throat of a person with or without pharyngeal symptoms, it is conceivable that the organism may have entered through the pharynx in some cases in which the route of invasion has not been established.

15. (*a*) Dmochowski, Z.: Beitrag zur Lehre über die pathogenen Eigenschaften des Friedländer'schen Pneumococcus, Zentralbl. f. Bakt. (Abt. 1) **15**:581 (April 27) 1894. (*b*) Sicard, A., and Pluvinage, R.: Méningite à pneumobacilles de Friedländer, Presse méd. **45**: 1800 (Dec. 15) 1937.

16. Jassniger, K.: Der Pneumococcus Friedländer als Erreger der eitrigen Meningitis cerebrospinalis, Zentralbl. f. Bakt. (Abt. 1) **30**:1 (July 12) 1901.

17. Dufourt, A.; Delattre and Bonnet: Méningite traînante à pneumo-bacille de Friedländer chez un nourrisson, Lyon méd. **138**:375 (Sept. 26) 1926.

18. Siredey, A.; Lemaire, H., and de Jong: Méningite cérébro spinale à pneumo-bacille de Friedländer, Bull. et mém. Soc. méd. d. hôp. de Paris **34**:258 (July 26) 1912.

Associated Complicating Conditions.—In the adult patients of Weichselbaum,[9] Rénon and Blamoutier,[19] Rothschild[6] and Menetrier and Bertrand-Fontaine[20] sugar was found in the urine, while Robertson's patient[18a] was known to have diabetes. Brunner's patient[21] had cirrhosis of the liver, and autopsy of our patient showed carcinoma of the prostate. Some other patients were thought to have been alcoholic addicts. The infant patients of Beitzke[14a] and Papandrea[22] had congenital syphilis. Two newborn infants with the disease were found to have intracranial hemorrhages.[23] It seems likely that debilitating conditions may predispose to the development of Friedländer's bacillus meningitis.

Diagnosis.—The usual signs and symptoms of meningitis are present in adults but may be lacking in infants. The diagnosis is a purely bacteriologic one and rests on the finding of the organism in smears and cultures of the spinal fluid. Of 19 cases of Friedländer's bacillus meningitis, including our own and others from the literature in which exact data were given, direct smears of the spinal fluid at the time of the first lumbar puncture were negative in 5 instances. Thus in about one fourth of these cases organisms were not found in the first smear. This fact is of considerable importance, since the failure to demonstrate organisms in smears of purulent spinal fluid when a diagnosis has not been made is usually considered strongly suggestive of meningococcic infection. Petechial hemorrhages occurring when Friedländer's bacillus septicemia is present may further confuse the picture, as in the case here reported. We have encountered 3 other cases of Friedländer's bacillus meningitis in which the initial diagnosis was uncertain enough so that antimeningococcus serum was given.[24] Cultures of the spinal fluid from the first lumbar tap were positive in 15 of 17 cases.

The spinal fluid is in no way characteristic, showing the usual changes of a purulent meningitis, with the cells in the exudate predominantly polymorphonuclear and an increased protein content and a diminished sugar content.

The demonstration of extrameningeal foci, such as otitis media, mastoiditis or sinusitis, may be suggestive if Friedländer's bacillus is shown to be the causative agent of such processes. Presence of the organism in cultures of material from the throat, of the urine or of the blood may supply additional evidence. Friedländer's bacilluria was observed in 1 fatal case[25] besides our own in which a blood culture

19. Rénon, L., and Blamoutier, P.: Un cas de méningite cérébrospinale à pneumobacille de Friedländer d'origine otitique, Ann. de méd. **9**:119 (Feb.) 1921.

20. Menetrier, P., and Bertrand-Fontaine: Sur un cas de méningite à pneumobacille du Friedländer à évolution suraigue, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:114 (Feb. 1) 1924.

21. Brunner, C.: Zur pathogenen Wirkung der Bacillus Friedländer. Ein Fall von acut metastasirender Allgemeininfektion nach Otitis media und Empyem des Proc. mastoides, München. med. Wchnschr. **43**:286 (March 31) 1896.

22. Papandrea, F.: Su due casi di meningite da diplobacillo di Friedländer, Pediatria **35**:371, 1927.

23. (*a*) Bonhoff, H., and Esch, P.: Ueber einen Fall von Meningitis purulente beim Neugeborenen infolge rechtseitiger eitriger Mittelohrentzündung, Ztschr. f. Geburtsh. u. Gynäk. **70**:886, 1912. (*b*) Slobozianu, H., and Ionescu, V. T.: La méningite àpneumobacilles de Friedländer chez les nouveaux-nés, Nourrisson **28**:153 (July) 1940.

24. (*a*) Elias, F.: Meningitis beim Säugling durch den Bacillus pneumoniae Friedländer [case 1], Deutsche med. Wchnschr. **50**:578 (May 2) 1924. (*b*) Lion, G., and Minvielle: Un cas de méningite suppurée à bacille du type Friedländer, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:286 (March 7) 1924. (*c*) Leenhardt, E.; Boucomont, J., and Balmès, J.: Deux cas de méningite à pneumobacille de Friedländer, Arch. Soc. d. sc. méd. et biol., Montpellier **18**:167 (April) 1937.

25. Comte; Lévy-Bruhl, M., and Dany: Un cas de méningite à pneumobacille de Friedländer avec septicémie, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:139 (Feb. 2) 1931.

was positive. We have found records of blood cultures of 10 patients with Friedländer's bacillus meningitis. Five of these, including the one here reported on, had positive cultures, and all these patients died.[26] Of the 5 with negative blood cultures 2 survived,[27] while a third, a 17 day old infant reported on by Elias [24a] (case 2), appeared on the way to recovery, only to die in a nursery outbreak of "influenzal pneumonia." The other 2 patients [28] died of meningitis, the first despite sulfapyridine therapy.

Prognosis and Chemotherapy.—Friedländer's bacillus causes a particularly malignant type of meningitis, which until recently was almost always fatal. In the available literature published prior to the introduction of the sulfonamide drugs, Rothschild's case [6] is the only incontestable nonfatal case of purulent meningitis we have encountered in which Friedländer's bacillus was recovered from the spinal fluid and adequate details of its bacteriologic identification given. In this case meningitis was secondary to otitis media, mastoiditis and subdural abscess, with recovery after operation.

Since the advent of the sulfonamide compounds several patients with Friedländer's bacillus meningitis have been cured. Lombard and Mondzain-Lemaire [29] discussed a patient who apparently had a mixed meningeal infection after a head injury and recovered after treatment with sulfamidochrysoidine,[30] but the criteria for the bacteriologic diagnosis were not described. Robertson [18] has recently reported a case in which a 49 year old man was cured with sulfapyridine. Friedländer's bacillus was found not only in the spinal fluid but in cultures of material from the throat and maxillary sinuses, and recovery of this patient is all the more remarkable because he had diabetes. Montes and Real [1b] described a Cuban child of 2 years without demonstrable primary focus who was likewise cured after administration of sulfapyridine. Both of these patients received autogenous vaccine late in the course of treatment. Kolmer and Rule [8] gave sulfapyridine unsuccessfully to an adult in whom the disease was secondary to Friedländer's bacillus infection of the sphenoid, ethmoid and frontal sinuses, but, although initial improvement was noted, cultures and smears of the spinal fluid continued positive. After five days a relapse occurred, and the patient died on the eighth day of treatment. Julianelle [28] mentioned a case in which Friedländer's bacillus meningitis was cured with sulfadiazine, and Trevett, Nelson and Long [2b] briefly cited a case in which the disease was successfully treated by Hodes with the same drug.

Experimental studies on Friedländer's bacillus infections in animals have shown that sulfanilamide is practically ineffective against the organism, while sulfapyridine exerts a moderate activity.[31] Laboratory investigation suggests that

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26. (*a*) Brain, W. R., and Valentine, F. S. O.: A Case of Infection of the Meninges and Blood Stream by Bacillus Mucosus Capsulatus, Lancet **1**:855 (April 28) 1928. (*b*) Fothergill and Sweet.[5e] Sicard and Pluvinage.[15b] Comte, Lévy-Bruhl and Dany.[25]

27. Robertson.[18] Rothschild.[6]

28. Kolmer and Rule.[8] Leenhardt, Boucomont and Balmès.[24c]

29. Lombard, P., and Mondzain-Lemaire, S.: Méningite aiguë, septique, post-traumatique. Traitement par sulfamido-chrysoïdine. Guérison, Mém. Acad. de chir. **64**:926 (June 15) 1938.

30. A compound supposedly identical with the original prontosil (a hydrochloride of 4-sulfamido-2',4'-diaminoazobenzene).

31. (*a*) Gross, P.; Cooper, F. B., and Lewis, M.: Sulfanilamide Therapy of Friedländer's Infections of Mice, Proc. Soc. Exper. Biol. & Med. **39**:12 (Oct.) 1938. (*b*) Bliss, E. A.; Feinstone, W. H.; Garrett, A. W., and Long, P. H.: Sulfapyridine and Sulfanilamide in Experimental Pneumococcal, Meningococcal, Welch Bacillary, and Friedländer's Bacillary Infections in Mice, ibid. **40**:619 (April) 1939. (*c*) Kolmer and Rule.[8]

sulfadiazine surpasses its predecessors in the therapy of Friedländer's bacillus infections.[32] The choice of the appropriate drug is thus of the greatest importance.

If no organisms are found in smears of purulent spinal fluid from cases of undiagnosed meningitis, it would seem wise to use a drug with a wide range of action, such as sulfadiazine, since it may be effective against Friedländer's bacillus as well as against the meningococcus[33] and other more common causes of meningitis.

SUMMARY

A case of Friedländer's bacillus septicemia and meningitis in an old man with carcinoma of the prostate has been reported, and autopsy observations are described. The infection was so overwhelming that recovery could hardly have been expected, but the diagnosis was difficult and delayed and the treatment, accordingly misdirected, was not the best. The case is of interest because of the rarity of Friedländer's bacillus as a cause of meningitis, and particularly in view of the small number of reports in the American literature. The disease occurs chiefly in infants and in adults, often after the fourth decade of life. Frequently it is associated with other debilitating conditions. In occasional cases confusion with meningococcic meningitis may occur because of the presence of petechiae and the lack of organisms in smears of the spinal fluid. A few patients with meningitis due to Friedländer's bacillus have recovered after administration of sulfapyridine or sulfadiazine, while formerly the condition was almost always fatal. When the diagnosis is made or suspected vigorous treatment with one of these drugs is indicated. Experimental work with animals suggests that sulfadiazine may prove more effective than its predecessors against Friedländer's bacillus infections.

Vanderbilt University School of Medicine.

32. Feinstone, W. H.; Williams, R. D.; Wolff, M. S.; Huntington, E., and Crossley, M. L.: The Toxicity, Absorption, and Chemotherapeutic Activity of 2-Sulfanilamidopyrimidine (Sulfadiazine), Bull. Johns Hopkins Hosp. **67**:427 (Dec.) 1940.

33. (*a*) Dingle, J. H.; Thomas, L., and Morton, A. R.: Treatment of Meningococcic Meningitis and Meningococcemia with Sulfadiazine, J. A. M. A. **116**:2666 (June 14) 1941. Hodes, H. L., and Strong, P. S.: Treatment of Meningococcic Meningitis with Sulfonamides, ibid. **119**:691 (June 27) 1942. Rundlett, E.; Gnassi, A. M., and Price, P.: Meningococcic Meningitis: Prognostic Significance of the Spinal Fluid Sugar, ibid. **119**:695 (June 27) 1942. (*b*) Trevett, Nelson and Long.[2b]

SULFADIAZINE ADMINISTERED ALONE AND WITH ANTIPNEUMOCOCCUS SERUM IN THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA

NATHAN H. SHACKMAN, M.D.*
AND
JESSE G. M. BULLOWA, M.D.
Clinical Professor of Medicine, New York University College of Medicine, and Visiting Physician, Harlem Hospital and Willard Parker Hospital
NEW YORK

Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine), the pyrimidine analog of sulfapyridine, has been shown by Feinstone and his associates [1] in their experiments with mice to be less toxic than either sulfapyridine or sulfathiazole. They found the drug to be readily absorbed into the blood and rapidly excreted in the urine. Higher concentrations were obtained with sulfadiazine than with equivalent doses of sulfapyridine or sulfathiazole. Long and his co-workers [2] reported that sulfadiazine was less effective at equivalent concentrations than sulfathiazole in the treatment of experimental pneumococcic infections in mice. Osgood and Bullowa,[3] using tissue cultures, found sulfadiazine to be only one-quarter as effective against pneumococci as sulfapyridine and sulfathiazole in equivalent concentrations.

Studies on the action of sulfadiazine in human beings have been reported by various investigators.[4] With an associate we [5] have previously reported on the pharmacodynamics of the drug in man. It is well absorbed from the gastrointestinal tract. As a rule, most of the drug exists in the blood in the free form. It diffuses readily into the spinal, the pleural and the peritoneal fluid. Although the major portion of the drug is rapidly excreted in the urine, traces may be detected for as long as six days after ceasing administration. Approximately 65 per cent of the

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*Littauer Fellow in Pneumonia Research, Harlem Hospital.

From the Medical Service, Harlem Hospital, Department of Hospitals, New York city, and the Littauer Pneumonia Research Fund of New York University College of Medicine. These studies received additional support from the Metropolitan Life Insurance Company and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

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2. Long, P. H.; Bliss, E. A., and Ott, E.: Studies on Sulfadiazine, Bull. Johns Hopkins Hosp. **69**:297, 1941.

3. Osgood, E. E., and Bullowa, J. G. M.: Unpublished data.

4. (*a*) Plummer, N., and Ensworth, H. K.: Absorption and Excretion of Sulfadiazine, Proc. Soc. Exper. Biol. & Med. **45**:734, 1940. (*b*) Reinhold, J. G.; Flippin, H. F.; Schwartz, L., and Domm, A. H.: Absorption, Distribution and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, Am. J. M. Sc. **201**:106, 1941. (*c*) Peterson, O. L.; Strauss, E.; Taylor, F. H. L., and Finland, M.: Absorption, Excretion and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), ibid. **201**:357, 1941. (*d*) Sadusk, J. F., Jr., and Tredway, J. B.: Observations on Absorption, Excretion, Diffusion and Acetylation of Sulfadiazine in Man, Yale J. Biol. & Med. **13**:539, 1941. (*e*) Wheeler, C., and Plummer, N.: Sulfadiazine and Sodium Sulfadiazine: A Comparison of Certain of Their Clinical and Pharmacological Values, Ann. Int. Med. **16**:269, 1942.

5. Ratish, H. D.; Shackman, N. H., and Bullowa, J. G. M.: The Pharmacodynamics of Sulfadiazine in Man, New England J. Med. **226**:596, 1942.

dose given may be recovered from the urine, and about one third of this is conjugated. High concentrations in the blood may be obtained rapidly by intravenous, subcutaneous and intramuscular administration of the sodium salt. Sulfadiazine is less toxic than either sulfapyridine or sulfathiazole.

METHOD AND MATERIAL

We report herewith our experience with 232 patients with pneumococcic pneumonia treated with sulfadiazine and 70 patients with this condition treated with rabbit antipneumococcus serum in addition. These patients, admitted to the Pneumonia Service of Harlem Hospital from July 1, 1940 to June 30, 1941, were adults for whom the diagnosis of pneumonia was based on history and physical findings and confirmed by roentgen examination. Prior to the institution of therapy bacteriologic studies of the sputum and the blood were made in all cases, and ordinarily treatment was withheld until the type of pneumococcus was determined. However, when attempts at typing the pneumococcus had been unsuccessful for twenty-four hours, therapy was no longer withheld, and sulfadiazine was given.

Dose.—Most of the patients in this series received an initial dose of 4 or 5 Gm. of sulfadiazine followed by a dose of 1 Gm. every four or six hours. Some patients, those very ill, received an initial intravenous injection of 5 Gm. of sodium sulfadiazine followed by doses of 1 Gm. given orally or intravenously at four or six hour intervals. The administration of the drug was discontinued when the temperature fell and remained below 100 F. with a pulse rate below 90 per minute for eighteen to twenty-four hours. Sulfadiazine was not given again unless there was a substantial persistent rise in temperature. Forty-four patients, or 63 per cent, received serum and sulfadiazine simultaneously; 9 patients received them one day apart, and 17 of the patients received the therapeutic agents two or more days apart. Of the 17 patients, 10 received serum first, whereas 7 were given the drug before the serum. Of the patients who received serum first, 8 were given sulfadiazine in addition either because the serum failed to influence the course of the disease or because the temperature, having fallen to normal, rose. Six patients who received the drug first were given serum because of marked bacterial invasion of the blood.

Samples of blood for determining drug levels and making immunologic studies were drawn every two days or more frequently if indicated. Concentrations of sulfadiazine were determined by the method of Bratton and Marshall, using a photoelectric colorimeter.[6]

RESULTS

Patients Who Died.—Table 1 shows the gross mortality without taking into consideration the essential factors influencing it, such as age and day of illness on which therapy was begun. Of the 232 patients treated with sulfadiazine alone 31 died —a mortality of 13.4 per cent. Excluding those patients moribund on admission who died within twenty-four hours, the mortality is 8.3 per cent. Nine of 29 patients, or 31 per cent, with bacteremia died. Of these, 6 died within twenty-four hours, and when they are excluded, the mortality becomes 13 per cent. The total mortality for the patients undergoing combination therapy was 14.3 per cent. Only 1 patient, with bacteremia, died within twenty-four hours of admission to the hospital. The mortality for patients with bacteremia in this group was 22.2 per cent. Although this was lower than the total mortality for patients with bacteremia in the group treated with sulfadiazine alone, the difference is not in itself significant. The incidence of blood cultures positive for pneumococci among patients given both serum and sulfadiazine was twice as great as among patients given sulfadiazine alone. This is a statistically significant difference (R. D. E. = 2.5).[7]

6. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537, 1939.

7. The abbreviation R. D. E. signifies the ratio of difference to error. A figure of 2.0 or more indicates significance.

The most frequently encountered Pneumococcus in both groups was type III, which caused 42 of 232 infections (18 per cent) in patients treated with sulfadiazine alone and 20 of 70 infections (28.6 per cent) in patients given combined therapy. Pneumococcus type VII was next in frequency, accounting for 11.6 and 14.3 per cent of infections, respectively. Next in order of frequency were pneumococci of type I, type IV and type VIII. Of these most frequently encountered types in the sulfadiazine-treated group, Pneumococcus type IV showed the highest mortality, with 21 per cent (4 of 19), followed by Pneumococcus type I (17.4 per cent), Pneumococcus type III (16.6 per cent) and Pneumococcus type VIII (6.3 per cent). In the group given both sulfadiazine and serum 1 of 5, or 20 per cent, of the patients whose infecting organism was Pneumococcus type I or type III died. Of the patients with infection caused by Pneumoccus type VIII, 14.3 per cent (1 of 7) died. The lowest mortality among the more frequently occurring

TABLE 1.—*Analysis of Infections by Types of Causative Pneumococci*

Type of Pneumococcus	Treatment: Sulfadiazine — No. of Patients	Sulfadiazine — No. of Deaths	Sulfadiazine — Percentage of Deaths	Sulfadiazine + Serum — No. of Patients	Sulfadiazine + Serum — No. of Deaths	Sulfadiazine + Serum — Percentage of Deaths
I	23	4	17.4	5	1	20.0
	9*	2*	22.2*	3*	0*	0.0*
II	7	0	0.0	4	1	25.0
	1*	0*	0.0*	3*	1*	33.3*
III	42	7	16.6	20	4	20.0
	2*	2*	100.0*	2*	2*	100.0*
IV	19	4	21.0	4	0	0.0
	6*	2*	33.3*	1*	0*	0.0*
V	5	0	0.0	2	0	0.0
	0*	0*	0.0*	1*	0*	0.0*
VI	3	1	33.3			
	0*	0*	0.0*			
VII	27	2	7.4	10	0	0.0
	3*	1*	33.3*	2*	0*	0.0*
VIII	16	1	6.3	7	1	14.3
	1*	1*	100.0*	1*	0*	0.0*
Other types	90	12	13.3	18	3	16.6
	7*	1*	14.3*	5*	1*	20.0*
Total	232	31	13.4	70	10	14.3
	29*	9*	31.0*	18*	4*	22.2*
Total minus deaths in 24 hours	217	18	8.3	60	9	13.0
	23*	3*	13.0*	17*	3*	17.6*

* Bacteremia.

types in this study was in infections caused by Pneumococcus type VII in the group given both sulfadiazine and serum and by Pneumococcus type VIII in the group given only sulfadiazine. Among the patients with type II pneumococcus pneumonia, which is usually a severe infection, there were no deaths in the sulfadiazine-treated group of 7 patients and only in the group of 4 patients undergoing combined therapy, although 3 of these 4 patients were bacteremic.

Among the numerous factors that influence the prognosis for patients with pneumonia is the presence of specific soluble substance [8] in the blood. Eight patients in the sulfadiazine-treated group and 7 patients in the group given both sulfadiazine and serum had capsular carbohydrate in their blood (table 2). Pneumococcus type III was the most frequently occurring type in both groups. Approximately one half of the patients in both groups died. In the drug-treated group

8. This substance may also be referred to as capsular carbohydrate or capsular polysaccharide.

3 of the 4 patients who died had infections caused by Pneumococcus type III. One patient (1), a 38 year old Negro, was admitted on the sixth day of illness with signs of meningeal irritation in addition to pneumonia (spinal fluid was normal). The next day he became irrational and went into shock. He received a total of 17 Gm. of sulfadiazine. The concentration of the drug in the blood

TABLE 2.—*Pertinent Data on Patients with Capsular Carbohydrate in Their Blood*

Case No. and Age	Type of Causative Pneumococcus	Day of Illness		Blood Culture *	Day of Illness S. S. S.† Detected	Treatment		Rabbit Serum, Units	Precipitin Test	Comment	Outcome
		Admitted to Hospital	Therapy Begun			Total Dose of Sulfadiazine, Gm.	Blood Level, Mg. % Free Drug				
1, 38	III	6	6	Negative	8	17	5.2 8.5	...	Negative	.....	Died
2, 69	III	?	?	Negative	?	39	11.2 13.8 14.8	...	.....	Cardiac disease	Died
3, 50	III	10	11	Positive	..	7.5	Not determined	...	Negative	Colostomy for lymphogranuloma venereum	Died
4, 50	VIII	5	5	Positive	..	4	Not determined	...	Not done	Sterile effusion	Died
5, 29	XVI	5	6	Negative	8	40	6.6 7.9 6.7	...	Positive; 1:4	.....	Recovered
6, 62	VIII	3	..	Negative	8	15	5.4	...	Not done	.....	Recovered
7, 25	I	4	4	Positive	7	33	6.6 9.5	...	Positive; 1:4	.....	Recovered
8, 15	II	3	3	Negative	4	12	3.8 3.5 5.5	...	Not done	.....	Recovered
9, 56	III	?	?	Positive	?	4	Not determined	360,000	Not done	Hypertensive heart disease; rectal stricture; hepatitis	Died
10, 60	III	9 (?)	9 (?)	Positive	10	6	Not determined	245,000	Not done	.....	Died
11, 50	III	9 (?)	10 (?)	Not done	..	39	5.8 6.1	431,000	Negative	.....	Died
12, 42	VIII	9	11	Not done	10	21	9.0 14.0	334,750	Not done	.....	Died
13, 43	VII	1	3	Positive	10; 11; 12; 16	26	5.2 10.4 7.7 7.0	243,000	Ample	Sterile effusion	Recovered
14, 27	XIX	3	3	Positive	3; 4; 5; 6	37	7.5 10.9 10.1 13.0	297,500	Positive; 1:4	.....	Recovered
15, 16	V	?	?	Positive	?	77	5.0 6.8 7.3 9.6 7.1 3.9 2.8 3.4	520,000	Not done	Pericardial effusion	Recovered

* Negative (or positive) for pneumococci.
† Specific soluble substance.

on two occasions was 5.2 and 8.5 mg. per hundred cubic centimeters. He died on the fourth day of hospitalization. A second patient (2), a 69 year old man, for whom the date of onset of illness was unknown, received 39 Gm. of sulfadiazine; the concentration of the drug in the blood reached 14.8 mg. per hundred cubic centimeters. His blood was sterile on culture but gave a strong reaction for capsular carbohydrate. He became stuporous, and his cardiac rhythm became irregular and rapid. Although he seemed to respond well to digitalis, he died

eight days after admission to the hospital. His infection had not been controlled (the temperature remained elevated) in spite of adequate concentrations of sulfadiazine. The third patient with an infection caused by Pneumococcus type III (patient 3) was a 50 year old woman who in addition to pneumonia had had a colostomy done for lymphogranuloma venereum and was admitted in an emaciated state. Her blood contained pneumococci of type III as well as capsular carbohydrate. She received only 7.5 Gm. of sulfadiazine. The fourth patient (4) in the drug-treated group was a 50 year old man with bacteremia due to Pneumococcus type VIII and a sterile pleural effusion. Blood cultures were positive for the infecting organism on several occasions. He received only 4 Gm. of sulfadiazine and died thirty-two hours after admission. The 4 patients in this group who recovered had infections due to Pneumococcus type I, type II, type VIII and type XVI respectively. They were less severely ill than those who died. All but 1 were under 40 years of age; 3 of the 4 were admitted prior to the fifth day of their illness. All but the patient with the infection due to Pneumococcus type I had blood cultures negative for pneumococci.

Of the 7 patients in the group given both sulfadiazine and serum who had capsular carbohydrate in their blood, 4 died; 3 of these 4 patients (9, 10 and 11) had infections caused by Pneumococcus type III. All 3 were over 40 years of age, and therapy was begun late in the course of their illness. Two of them had bacterial invasion of the blood. One died three hours and another seven hours after therapy was started and had received only 4 and 6 Gm. of sulfadiazine, respectively, in addition to serum. The third patient received 39 Gm. of the drug and 431,000 units of rabbit serum. Two died too soon to permit blood levels of sulfadiazine to be determined; the third had a blood level of 6.1 mg. of free drug per hundred cubic centimeters. The fourth patient who died (patient 12) was a 42 year old woman with an infection due to Pneumoccus type VIII, for which therapy was begun on the ninth day of illness. The blood of 1 of the 4 patients who died was studied for precipitins, and none was found. The 3 patients in this group who recovered had infections due to Pneumococcus type V, type VII and type XIX, respectively. All had blood cultures positive for the infecting organism. Two of the 3 had precipitins in their blood after serum therapy.

All patients with infections due to Pneumococcus type III whose blood gave a reaction for specific soluble substance died regardless of the form of therapy. Three of these 6 patients had bacteremia as well. Six of a total of 15, or 40 per cent, of those patients who had demonstrable specific soluble substance in their blood had infections due to the type III pneumococcus. This pneumococcus accounted for 6 of the 8 deaths. That Pneumococcus type III produces capsular carbohydrate more abundantly than pneumococci of other types and that the presence of this substance in the blood of patients is of grave prognostic import has been previously shown in reports from this laboratory (Bukantz and associates[9]). The death rate among patients with detectable specific soluble substance in their blood is approximately four times greater than among those patients who do not have it.

An analysis of death rates in relation to age and to day of illness on which therapy was instituted is shown in table 3. In both therapy groups the largest mortality occurred in patients over 40 years of age first treated after the fifth day of illness; the mortality was about twice that for any of the three other categories in table 3. This last category contained the largest number of patients in both therapy groups — 40 per cent in the drug-treated group (93 of 232) and 34 per cent in the group given both sulfadiazine and serum (24 of 70).

9. Bukantz, S. C.; de Gara, P. F., and Bullowa, J. G. M.: Capsular Polysaccharide in the Blood of Patients with Pneumococcic Pneumonia, Arch. Int. Med. **69**:191 (Feb.) 1942.

Detailed case analyses for the patients who died are shown in tables 4 and 5. It will be seen that a number of the patients in both therapy groups died not of their pulmonary infection but of other unrelated conditions in which the pneumonia was a terminating event. In the sulfadiazine-treated group (table 4), 1 patient (26) had a coronary occlusion preceding pneumonia, and lobar pneumonia developed in another (patient 37) one day after a gastric resection for carcinoma. One patient (22) was admitted after an acute cerebral hemorrhage with a right hemiplegia, and pneumonia developed six days later; he died within twenty-four hours after institution of therapy. Still another patient (32) had a carcinoma of the esophagus. In patient 34 the complicating factor was severe scleroderma. Nine patients had cardiac disease of various degree, causation and duration. Of these, 2 patients were in mild congestive failure on admission to the hospital; of the remainder, 5 had diminution of cardiac reserve, such as dyspnea on effort, which contributed to the fatal outcome.

Patients Who Recovered.—In addition to the effect of a given therapeutic agent on the mortality of a disease, one must consider also its effect on the clinical course of the disease in the patients who recovered. In the sulfadiazine-treated group

TABLE 3.—*Relation of Age, Day of Illness on Which Therapy Was Started and Outcome*

	Treatment					
	Sulfadiazine			Sulfadiazine + Serum		
	No. of Patients	No. of Deaths	Percentage of Deaths	No. of Patients	No. of Deaths	Percentage of Deaths
Patients under 40, first treated on 1st to 4th day of illness	33 5*	1 0*	3.0 0.0*	9 3*	0 0*	0.0 0.0*
Patients under 40, first treated on 5th day of illness and later	66 7*	5 2*	7.6 28.6*	19 3*	1 0*	5.3 0.0*
Patients over 40, first treated on 1st to 4th day of illness	40 5*	5 1*	12.5 20.0*	18 5*	2 0*	11.1 0.0*
Patients over 40, first treated on 5th day of illness and later	93 12*	20 6*	21.5 50.0*	24 7*	7 4*	29.3 57.2*

* Bacteremia.

54 of 201 patients who recovered, or 26.9 per cent, had their disease terminated within twenty-four hours after the institution of therapy, with a fall in temperature below 100 F. and in pulse rate below 90 per minute as a criterion for the termination of the infection. Of the patients who recovered 118 of 201, or 58.7 per cent, became afebrile within forty-eight hours after receiving the first dose of sulfadiazine. The temperature and the pulse rate fell to normal in relation to the administration of the drug and not to the day of illness on which therapy was started. Of the patients who received both serum and sulfadiazine, 26 of the 60 who recovered, or 43 per cent, became afebrile within forty-eight hours after therapy was started.

In the drug-treated group the median dose of sulfadiazine for the patients who recovered was 20.7 Gm. Of these patients, 63 per cent received between 10 and 24 Gm. of sulfadiazine, whereas 34 per cent of those who died were in this dose range. There were 28 patients who received less than 10 Gm. of sulfadiazine; 12 of these recovered, and 16 died—this represents 6 per cent of the recoveries and 52 per cent of the deaths. The patients who received this dose group and who died were much more severely ill on admission than were the 12 who recovered —50 per cent of the former had bacteremia but none of the latter. Most of those who received less than 10 Gm. of the drug and died did so within twenty-four hours after therapy was begun.

TABLE 4.—*Case Analyses of Deaths Occurring Among Patients Treated with Sulfadiazine*

No. of Patient	Type of Pneumococcus	Age; Sex	Day of Illness on Which Therapy Started	Interval Between Beginning of Therapy and Death	Blood Culture *	S. S. S.† in Blood	Total Dose of Sulfadiazine, Gm.	Complications and Associated Conditions
16	I	67 ♀	6	13 hr.	Positive	Negative	8	
17	I	43 ♂	3	3 hr.	Positive	Not done	4	Cardiac decompensation; pulmonary edema
18	I	39 ♂	4	12 days	Negative	Negative	35.5	
19	I	78 ♀	7	19 days	Negative	Negative	21	Empyema; second degree burns
2	III	60 ♂	?	7 days	Negative	Positive	39	Cardiac disease
20	III	65 ♀	3	17 days	Negative	Negative	28	Pleural effusion; traumatic pneumothorax; hypertensive heart disease; adenoma of thyroid
21	III	65 ♀	? Late	28 hr.	Positive	Not done	8	Autopsy: cholecystitis; atheroma of aorta; myocardial fibrosis; fatty metamorphosis of liver; chronic pyelonephritis
1	III	38 ♂	6	60 hr.	Negative	Positive	17	Epilepsy
22	III	75 ♂	? Late	14 hr.	Negative	Negative	7	Hypertensive and arteriosclerotic heart disease; cerebral hemorrhage
23	III	32 ♀	? Late	14 hr.	Negative	Not done	6	Coma on admission; asthmatic bronchitis
3	III	50 ♀	11	36 hr.	Positive	Positive	7.5	Autopsy: esophageal varices; chronic duodenal ulcers; colostomy for lymphogranuloma venereum
24	IV	62 ♂	?	7 hr.	Positive	Negative	6	Autopsy: fibrinous pleurisy; cirrhosis of liver; cloudy swelling of kidney; coronary and aortic atherosclerosis
25	IV	52 ♀	15	10 hr.	Positive	Negative	6	Treatment begun late in course of illness
26	IV	65 ♀	?	10 hr.	Not done	Not done	7	Coronary occlusion
27	IV	53 ♀	?	36 hr.	Negative	Negative	14	Effusion
28	VI	65 ♀	?	8 days	Negative	Negative	18	Emphysema; chronic bronchitis; coronary disease; decubitus ulcers
29	VII	32 ♀	6	26 hr.	Positive 6 times	Negative	10	Overwhelming bacteremia
30	VII	33 ♀	?	13 hr.	Negative	Negative	9	
4	VIII	50 ♂	5	3 hr.	Positive	Positive	4	Sterile effusion; avitaminosis
31	IX	54 ♂	10	46 hr.	Negative	Negative	13	Putrid empyema secondary to ruptured pulmonary abscess
32	IX	64 ♂	?	35 hr.	Negative	Negative	14	Carcinoma of esophagus
33	X	64 ♀	?	8 days	Negative	Not done	14	
34	XI	40 ♀	4	49 hr.	Negative	Negative	16	Scleroderma; Addison's disease ?
35	XII	50 ♀	9	4½ days	.....	Negative	18	Cardiac disease
36	XXI	43 ♂	?	13½ days	Negative	Negative	28	Hypertensive cardiovascular disease
37	XXV	45 ♂	?	96 hr.	.....	.....	7	Complication after operation for carcinoma of stomach
38	XXXIII	48 ♀	14	5 hr.	Negative	Not done	4	Hepatomegaly, cause unknown
39	XXXIV	63 ♂	14	15 hr.	Negative	Not done	7	Delirium tremens; autopsy: syphilitic aortitis, fatty degeneration of liver, coronary atherosclerosis
40	XVIII A	38 ♂	5	3 hr.	Positive	Not done	6	Rheumatic heart disease
41	III B. F. A.	45 ♂	3 ?	16 hr.	Negative	B. F. A.‡	8	Autopsy: fibrinous pleurisy; fatty metamorphosis of kidney; benign nephrosclerosis
42	VIII XXXIV	69 ♀	4	25 hr.	Negative	Negative	10	Autopsy: purulent empyema; fibrinous pericarditis

* Positive (or negative) for pneumococci.
† Specific soluble substance.
‡ Bacillus Friedländer A.

Many variables are involved which do not easily lend themselves to evaluation, so that one cannot arbitrarily state what constitutes the optimum dose. The virulence of the organisms and their susceptibility to the drug, inhibiting or enhancing substances in the blood, the number of bacteria in the local lesion, bacterial invasion of the blood and complications are but a few of the factors involved. We may, however, suggest that 10 Gm. of sulfadiazine is, in the majority of cases, insufficient to control pneumococcic pneumonia and that doses of 10 to 24 Gm. are adequate for two thirds of patients with such pneumonia.

In attempting to determine an adequate therapeutic concentration of the drug in the blood similar difficulties are encountered. There is great variability in the blood levels obtained with the same dose of drug in different patients and

TABLE 5.—*Case Analyses of Deaths Occurring Among Patients Treated with Sulfadiazine and Serum*

No. of Patient	Type of Pneumococcus	Age; Sex	Day of Illness: Sulfadiazine Therapy Started	Day of Illness: Serum Given	Interval Between Therapy and Death	Blood Culture*	S. S. S.† in Blood	Total Dose of Sulfadiazine, Gm.	Total Dose of Serum, Units	Precipitin Test	Complications and Associated Conditions
43	I	74 ♂	23	23	29 hr.	.....	Negative	6	214,500	Not done	Admitted in state of pulmonary edema
44	II	41 ♂	18 23	7	17 days	Positive	Negative	47 10	200,000	Positive	Treatment begun late in course of illness
45	III	40 ♂	3	3	9 days	Negative	Negative	47	850,000	Positive	
10	III	69 ♀	? 9	? 9	7 hr.	Positive	Positive	6	245,000	Not done	Inadequate late treatment
11	III	50 ♂	? 9	? 10	7 days	.....	Positive	39	431,000	Negative	Azotemia
9	III	56 ♀	?	?	3 hr.	Positive	Positive	4	360,000	Negative	Arteriosclerosis; hypertensive heart disease; hepatitis; lymphogranuloma venereum with rectal stricture
12	VIII	42 ♀	9	11	4 days	Negative	Positive	21	334,750	Not done	Treatment begun late in course of illness
46	XXXIII	49 ♂	5	6	34 hr.	Positive	Negative	10	205,000	Not done	Circulatory failure
47	XXXIII	36 ♀	8	8	61 hr.	Negative	Negative	16	150,000	Positive	Treatment begun late in course of illness
48	XXIII; B. F. A.‡	46 ♂	3	3	32 hr.	Negative	Negative	12	120 cc. B. F. A. serum	Not done	Autopsy: hepatomegaly; fibrinous pleurisy; atherosclerosis of aorta; chronic myocarditis

* Positive (or negative) for pneumococci.
† Specific soluble substance.
‡ Bacillus Friedländer A.

in the same patient at different times—age and degree of absorption, conjugation and renal elimination are some of the factors influencing blood levels. In addition, pneumococci, even of the same type, vary in susceptibility to a given sulfonamide compound (as shown by in vitro experiments). In the sulfadiazine-treated group the largest number of patients who recovered had a blood level between 7 and 8 mg. of free drug per hundred cubic centimeters as their highest concentration. Of the patients who recovered (125 of 201), 62 per cent had blood levels ranging from 5 to 10 mg. of free drug per hundred cubic centimeters, whereas 34 per cent of the patients who died had the same concentration range. The median of the highest concentration of all the patients who recovered was 8.7 mg. per hundred cubic centimeters. The median initial concentration among the patients who recovered was 7.4 mg. per hundred cubic centimeters. In 24 per cent of the

total number of patients in the sulfadiazine-treated group (55 of 232) the initial concentration was the highest.

In the group given both sulfadiazine and serum there were 6 patients whose blood was not studied, so that observations are based on the remaining 4. The median highest concentration in the 58 patients who recovered was 8.4 mg. per hundred cubic centimeters. Of these patients, 62 per cent had blood levels of free drug ranging from 6 to 10 mg. per hundred cubic centimeters; 3 of the 7 patients who died had the same concentration range.

Rises in Temperature.—In 167 of 201, or 83 per cent, of the patients who recovered after treatment with sulfadiazine alone the temperature and the pulse remained down after administration of the drug had been discontinued. Thirty-four patients had a rise in temperature after it had remained below 100 F. for about twenty-four hours. The temperatures of 5 of the 32 patients whose temperature charts were analyzed rose while they were still receiving the drug; the temperatures of the remaining patients rose after administration of sulfadiazine had been stopped. The shortest interval between discontinuance of the drug and rise in temperature was eight hours; the longest, fourteen days. Most (24 of 32) of the secondary rises in temperature occurred within seventy-two hours after sulfadiazine therapy had been discontinued. Four patients had a rise in temperature on one observation only, whereas the remainder had a sustained temperature for a period varying from eight hours to eleven days. In more than half the patients the temperature fell within forty-eight hours after it had risen. Seven patients had more than one bout of fever, with normal temperature between. Most of the febrile episodes were relatively mild; only 7 patients had temperatures above 102 F. Sulfadiazine was readministered to only 4 patients. The additional sulfadiazine was not especially effective; only 1 patient showed a prompt fall in temperature. It was found that 3 patients had sterile pleural effusions, 1 had sinusitis and another had purulent conjunctivitis. In the case of 2 others administration of the drug was discontinued while the temperature and the pulse were still elevated. No explanation could be found for the rise in temperature of the remaining 25 patients.

In the group given both sulfadiazine and serum 16 patients, or 27 per cent, had a rise in temperature; in 2 of these the rise occurred during the administration of the drug but after the serum had been given. The interval between discontinuance of therapy (drug) and rise in temperature varied from twelve hours to eleven days. In 50 per cent of the patients the febrile episode occurred within forty-eight hours after cessation of therapy. Seven patients had more than one febrile period, with normal temperature intervening. Temperatures above 102 F. occurred in 10 patients. The temperature remained elevated from eight hours to nineteen days, and in half the patients the elevation lasted for more than four days. One patient was given additional drug for four days without effecting a drop in temperature. Sterile fluid was obtained by thoracentesis several days later. The febrile reactions were due to sterile effusion in 2 instances and to serum sickness in 5. Spread of the infection to another lobe, as well as development of sterile fluid on the side of the original infection, was the cause of the rise in temperature in 1 patient (49, fig. 1). In another patient concomitant tuberculosis was responsible for the febrile period. In 2 patients infection of the urinary tract due to Escherichia coli was the probable cause. The rise in temperature of the remaining 5 patients in the group could not be explained.

It is of interest to note that 30 per cent of the febrile episodes in the sulfadiazine-treated group and 50 per cent of those in the group given both sulfadiazine and

serum occurred in patients whose infecting organism was Pneumococcus type III. This incidence is greater than would be expected from the relative occurrence of type III pneumococcus infections in the whole series. The reasons for this are not obvious.

Complications.—The incidence of complications (table 6) related to pneumococcic lobar pneumonia was found to be 4.7 per cent (in 11 patients of 232) in the sulfadiazine-treated group and 14.3 per cent (in 10 patients of 70) in the group given both sulfadiazine and serum. There were 5 patients with empyema in the drug-treated group, with 3 deaths, and 2 with this complication in the other group, without fatality. In the former group all patients who died and 1 who recovered had fluid in their pleural cavities on admission to the hospital. In the remaining patient in this group and in the 2 patients in the other group the

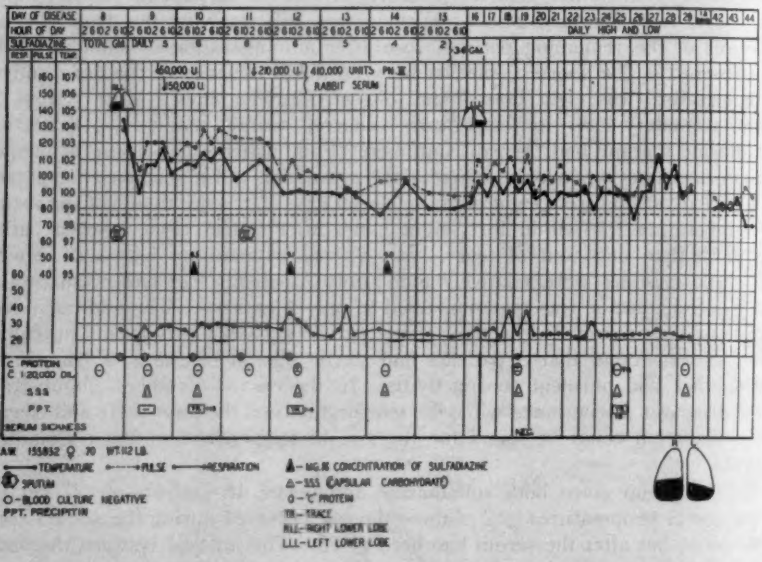


Fig. 1 (patient 49).—The clinical chart showing the course of illness in a 70 year old Negress with lobar pneumonia due to a type III pneumococcus; the temperature and the pulse after having been depressed rose because of development of fluid on the side of the original pneumonia and consolidation on the opposite side. C protein is the substance precipitated by the C polysaccharide, or somatic carbohydrate, of the pneumococci.

TABLE 6.—*Complications*

Complication	Treatment: Sulfadiazine — Total No. of Patients	Sulfadiazine — No. of Deaths	Sulfadiazine + Serum — Total No. of Patients	Sulfadiazine + Serum — No. of Deaths
Empyema	5 2*	3 0*	2 2*	0 0*
Sterile effusion	6 1*	2 2*	7 2*	0 0*
Pericardial effusion	..	..	1*	0

* Bacteremia.

effusion was discovered during treatment. All the patients in both groups who recovered had blood cultures positive for the infecting pneumococcus, whereas those who died did not have bacterial invasion.

One of the sulfadiazine-treated patients who died (patient 19) was a 78 year old Negress who was admitted on the fifth day of her illness with a type I pneumococcus lobar pneumonia and effusion. Repeated thoracic taps yielded purulent fluid from which the pneumococcus grew. In addition, she had second degree burns of the right side of the chest and abdomen and the right thigh. Because of her age and debility she was treated by repeated aspirations and instillation of sulfadiazine into the pleural cavity; she also received the drug orally. Specific soluble substance was detected in the thoracic fluid but not in her blood. The blood, tested on one occasion, did not show precipitins. After apparent improvement the patient died in shock nineteen days after admission to the hospital.

The second patient (42) was a 69 year old emaciated Negress admitted on the third day of her infection; she died forty-eight hours later. A diagnosis of pneumonia of the lower lobe of the right lung was made on admission, and Pneumococci of type VIII and type XXXIV were recovered from the sputum. A clinical impression of enlargement of the heart was confirmed by roentgen examination. Fluid in the chest was not suspected ante mortem. At autopsy 200 cc. of purulent exudate in the right pleural cavity, fibrinous pericarditis and cardiac hypertrophy were encountered.

The third patient (27), a 53 year old Negress, was brought to the hospital after three weeks of illness at home. Pleural effusion was found on admission, and thoracentesis yielded serosanguineous fluid from which Pneumococcus type IV was isolated. The patient received a total of 14 Gm. of sulfadiazine by mouth; the concentration of free drug in the blood was 5.6 mg. per hundred cubic centimeters on one occasion. The patient was dehydrated. She became semicomatose and died eighty-four hours after admission.

One of the patients (50) in the sulfadiazine-treated group who recovered was a 39 year old man admitted on the second day of his disease with a type VII pneumococcus pneumonia and a blood culture positive for the infecting organism. The organism was recovered from his thoracic fluid on several occasions; capsular polysaccharide was detected once in the fluid. In addition to 47 Gm. of sulfadiazine given orally, he received 15 Gm. of the drug in divided doses by pleural injection. Precipitins were found in his blood on several occasions. He made an uneventful recovery without surgical intervention and was discharged cured thirty-five days after admission to the hospital. His blood picture will be discussed in another portion of this paper.

The other recovery in this group was made by a patient (51) with type I pneumococcus empyema who had had a rib resection performed fourteen days after admission. His blood culture was positive for Pneumococcus type I on one occasion. Prior to thoracotomy he had received 19 Gm. of sulfadiazine, but none after it. His temperature dropped to normal on the third day after operation. Recovery was uneventful.

The 2 patients with empyema who received serum and sulfadiazine had infections due to type IV and type VII organisms, respectively. Both had bacterial invasion of their blood. They had ample circulating antibodies in the blood, but neither had had capsular polysaccharide in the blood or the thoracic fluid. The patient with the type IV pneumococcus infection (patient 52) was admitted on the fourth day of his infection, and the presence of fluid in his chest was suspected

five days later. Numerous attempts at thoracentesis were unsuccessful. Because of roentgen evidence thoracotomy was performed one month after admission and a paravertebral empyema on the right side was found. Prior to the operation the patient received 36 Gm. of sulfadiazine and 620,000 U. S. P. units of rabbit antipneumococcus serum. His temperature fell to normal on the first day after operation, and he was discharged thirty days later.

The other patient (53), a 33 year old man, was admitted two days after the onset of his illness. A thoracic tap done three days later yielded cloudy brownish fluid in which type VII pneumococci were present. He was at first treated by closed intercostal drainage and irrigations with 1:3,300 azochloramide with a tertigol penetrant (sodium tetradecyl sulfate), but a rib resection was finally performed, and he recovered. He had received 23 Gm. of sulfadiazine in addition to 210,000 units of rabbit serum.

There were 6 patients with sterile pleural effusions in the sulfadiazine-treated group, with 2 deaths, and 7 in the other group, without fatality. In the former group 3 patients had fluid in the pleural spaces on admission to the hospital. In the latter group signs of fluid developed in all but 2 patients during therapy. One of the patients who succumbed (patient 20) was a 65 year old Negress admitted on the second day of her illness with a diagnosis of pneumonia of the lower lobe of the right lung and pleural effusion. Pneumococcus type III was found in her sputum. Thoracentesis the next day yielded sterile serous fluid containing 9,000 white blood cells per cubic millimeter, predominantly mononuclear cells. Two days after the third thoracic tap (fifteenth day of hospitalization) a tension pneumothorax developed which necessitated decompression by underwater drainage. The patient seemed to be improving but died suddenly three days later, markedly dyspneic. An electrocardiogram taken three days after admission to the hospital showed evidence of myocardial damage. She received a total of 28 Gm. of sulfadiazine, and on two occasions its concentration in the blood was 8.9 and 13.6 mg. per hundred cubic centimeters. No postmortem examination was done.

The other fatality occurred in a 50 year old white man (patient 4) admitted on the fifth day of his illness; he died thirty-two hours later. He had fluid in his right pleural cavity from the base almost to the apex, with a moderate shift of the mediastinum to the opposite side. Three blood cultures were positive for Pneumococcus type VIII. The day after admission 100 cc. of serosanguineous fluid was withdrawn from the chest. The organism was found in the thoracic fluid on culture, but it probably was present in the blood which was mixed with the fluid. The patient received only 4 Gm. of the drug, when he died in a comatose state and in pulmonary edema. Antibody studies were not done.

An uncommon complication was encountered in a 16 year old boy (patient 15, fig. 2), who gave a three day history of abdominal pain and vomiting. Signs of consolidation were present over the upper lobe of the right lung. His sputum and blood contained pneumococcus type V. He received three courses of therapy with sulfadiazine, totaling 77 Gm., and 520,000 U. S. P. units of rabbit antipneumococcus. His response to therapy was poor. A pericardial friction rub was heard sixteen days after admission. Roentgenograms revealed progressive enlargement of the cardiac shadow. Pericardial taps yielded small amounts of hemorrhagic fluid, which was sterile on culture. His blood contained both Pneumococcus type V and its capsular carbohydrate. He made a slow but apparently complete recovery and was discharged after seventy-six days in the hospital. His hematologic response will be presented elsewhere in this paper.

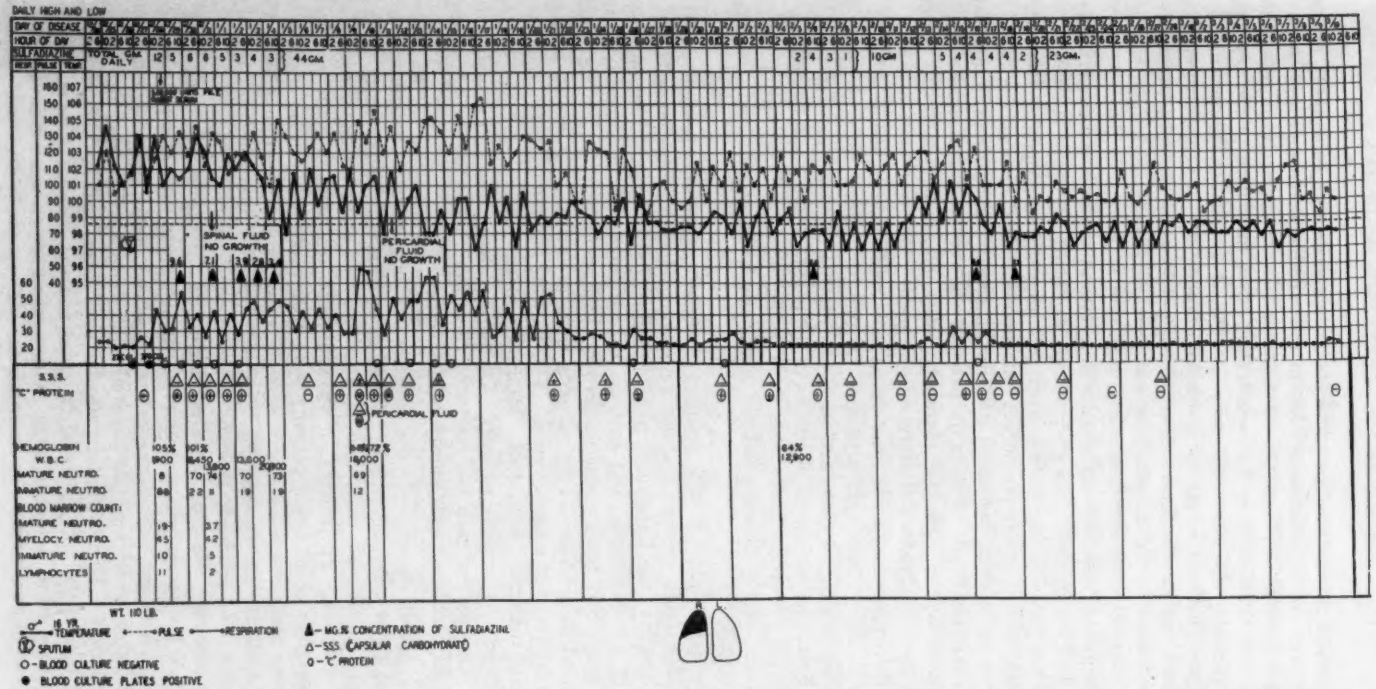


Fig. 2 (patient 15).—The clinical chart of a 16 year old boy with a type V pneumococcus pneumonia of the upper lobe of the right lung and pericardial effusion. Initial leukopenia (the percentage of granulocytes remained large and the bone marrow active) responded well to chemotherapy.

Associated Diseases.—The incidence of associated or concurrent disease was 18.5 per cent (in 43 patients of 232) in the sulfadiazine-treated group and 13 per cent (in 9 patients of 70) in the other group. In the former group there were 18 patients with heart disease, 9 of whom died; they have been previously discussed. Of the patients who recovered, only 2 were in congestive failure (mild) and 2 others gave histories of previous hospitalizations for decompensation. In 1 of the patients, admitted in heart failure, lobar pneumonia developed twenty-five days after admission to the hospital; he recovered. He was readmitted nine months later in congestive cardiac failure and died.

In the group given both sulfadiazine and serum there were 3 patients with cardiac disease, 1 of whom died. She gave a history of heart disease of one year's duration and did not have cardiac failure when admitted to the hospital. Her death was attributable to her severe pulmonary infection due to Pneumococcus type III. In addition to bacteremia, her blood contained capsular carbohydrate in abundance up to the time of her death. One of the patients who recovered had signs of decompensation on admission. He had rheumatic heart disease with auricular fibrillation; his response to digitalis and diuretics was good.

In the entire series there were 10 patients with diabetes mellitus, all of whom recovered. Three had mild acidosis. Of the 10, 7 knew they had had diabetes for varying lengths of time, and in 3 patients the disease was discovered during routine urinalysis and chemical studies of the blood. Only 3 had moderately severe diabetes; the remainder had a mild form of the disease. For most of the patients the presence of the diabetes did not materially increase the length of their stay in the hospital.

There were 6 patients with pulmonary diseases other than pneumonia, of whom 2 had tuberculosis (fibrotic), 2 had asthma and 1 each had bronchitis and a pulmonary abscess; the last-named patient died. One patient had an advanced carcinoma of the esophagus, and another had carcinoma of the stomach; both died. Two patients had benign nephrosclerosis; hydronephrosis on the right side was encountered in another. Two patients were pregnant, 1 of whom was at term and was delivered of a normal child. Two patients had lymphogranuloma venereum with rectal strictures; both died. Multiple duodenal ulcers were also encountered post mortem in 1 of these patients. Of the 2 patients who had delirium tremens, 1 died. One patient each had fractured ribs, peptic ulcer, severe scleroderma and bacteremia associated with paratyphoid fever.

Toxic Manifestations.—In the entire series there were 23 patients who experienced nausea or vomiting or both; this is an incidence of 7.6 per cent. One patient complained of nausea only, and another vomited without experiencing nausea. Of the remaining 21 patients, 7 showed these reactions on only one occasion. The complaints of all but 3 patients were relatively mild. In no instance in this series were these reactions severe enough to warrant discontinuing drug therapy. In most patients the nausea and vomiting appeared after the first few doses of sulfadiazine and subsided, though therapy was continued. Those who vomited prior to receiving the drug were not included. In the entire series no gross or microscopic hematuria was encountered, though crystals were frequently found in the urine. Nitrogen retention (creatinine 2.5 mg. per hundred cubic centimeters and urea nitrogen 95 mg. per hundred cubic centimeters) developed in 1 patient during therapy. Urea clearance several days later was 75 per cent of normal. Without special therapy the renal function and the chemical aspects of the blood returned to normal in several days. One patient experienced a severe chill and a sharp drop in temperature to normal, as well as marked clinical improvement,

after receiving about 1 Gm. of sodium sulfadiazine by continuous infusion. This reaction was probably not due to the drug, since administration of 5 Gm. of sodium sulfadiazine in 1 per cent concentration in solution of sodium chloride some time later to the same patient failed to produce it. We have not observed any mental reactions (in this series) definitely attributable to the drug. We observed neither leukopenia nor anemia as a result of the drug therapy. There were, however, 3 patients who had a low total white cell count but were given sulfadiazine because it was felt that the leukopenia was due to the severity of the infection and that intensive immediate therapy was indicated. One patient with type VII pneumococcus pneumonia had a total white cell count of 2,950, with 33 per cent segmented and 53 per cent nonsegmented neutrophils. A smear of his bone marrow showed myelocytic activity. He received a total of 47 Gm. of sulfadiazine. His white cell count rose to 11,000 during therapy. A second patient had lobar pneumonia caused by a type II pneumococcus, bacteremia and pleural effusion. His blood showed 6,000 white cells, with 40 per cent segmented and 12 per cent nonsegmented neutrophils. Because his bone marrow showed marked myelocytic hyperplasia, he was given sulfadiazine. In addition to 33 Gm. of the drug, he received 200,000 U. S. P. units of rabbit antipneumococcus serum. On the fifth day of therapy his white cell count rose to 27,500, and before discharge it was 11,425. The third patient was a 16 year old boy (patient 15) with lobar pneumonia caused by a type V pneumococcus and pericarditis (fig. 2). His initial white cell count was 1,900, with 8 per cent mature polymorphonuclears and 84 per cent nonsegmented neutrophils. He received three courses of sulfadiazine therapy totaling 77 Gm., as well as 520,000 U. S. P. units of rabbit antipneumococcus serum. Three days after therapy was started his white cells numbered 8,450, of which 70 per cent were mature neutrophils. Within a week his white cell count had risen to 20,900. Sternal puncture disclosed an active bone marrow. It should be noted that all 3 patients, though having a low total white cell count, had a high percentage of granulocytes, with a marked shift to the left. They also had active bone marrow. These findings are evidence of severe infection and are indications for intensive chemotherapy. All 3 patients recovered.

One patient of the entire 302 considered in this report had a rash that was probably due to sulfadiazine. She was a 42 year old Negress with a type XXIV pneumococcus pneumonia who had received 37 Gm. of the drug. Seven days after therapy had been stopped an erythematous pruritic rash developed over her face and chest accompanied by a rise in temperature which ranged between 101 and 103.2 F. for thirty-six hours. She had received no other medication that might have been responsible for this phenomenon. Although the rash and fever occurred a week after the last dose of the drug had been given, it was probably a delayed toxic manifestation.

COMMENT

In our group of patients with pneumonia for whom pneumococci could be typed the mortality of those treated with sulfadiazine alone is about the same as that reported by other investigators [10] for similar series of patients, although it is con-

10. (*a*) Flippin, H. F.; Rose, S. B.; Schwartz, L., and Domm, A. H.: Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcic Pneumonia: A Progress Report on Two Hundred Cases, Am. J. M. Sc. **201**:585, 1941. (*b*) Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects on Four Hundred and Forty-Six Patients, J. A. M. A. **116**:2641 (June 14) 1941. (*c*) Dowling, H. F.; Hartman, C. R.; Sugar, S. J., and Feldman, H. A.: The Treatment of Pneumococcic Pneumonia with Sulfadiazine, ibid. **117**:824 (Sept. 6) 1941. (*d*) Flippin, H. F.; Rose, S. B.; Schwartz, L., and Domm, A. H.: Treatment of Pneumococcic Pneumonia with Sulfadiazine and Sodium Sulfadiazine, War Med. **2**:284 (March) 1942.

siderably higher than that reported by Billings and Wood [11] (1.3 per cent). The incidence of bacteremia in our group was somewhat less than in the first four of the five series referred to and greater than in the last. The incidence of patients over 40 years of age was about the same as that reported by the other authors. In our group 68 per cent of the patients were admitted to the hospital late in the course of illness, whereas only 39 per cent of the series reported by Flippin and associates,[10a] 44 per cent of the series reported by Dowling and his co-workers [10c] and 33 per cent of the series reported by Flippin and his associates [10d] in a subsequent paper fell into that category. Because of the possibility that the delay of treatment for some hours to allow for specific typing of the infecting pneumococcus may have influenced our mortality rate, we have since July 1941 been instituting chemotherapy as soon as a diagnosis of pneumonia is made. Before therapy is begun, specimens of sputum and blood are obtained for study. In those cases in which typing is successful type-specific serum is then given to alternate patients unless they have already responded to chemotherapy.

It is the practice of our service to discontinue chemotherapy entirely after the temperature and the pulse have fallen to normal and remained so for eighteen to twenty-four hours. In this series it was found that the temperatures of 83 per cent of the patients treated with sulfadiazine alone remained normal (below 100 F.) after therapy was discontinued. In the remaining 17 per cent, who had a secondary rise in temperature, the febrile episodes were usually relatively mild and of short duration. Our method of terminating chemotherapy is more economical and probably results in a lessened incidence of toxic reactions than does the method of tapering.

In our present series, as well as in those of the other investigators, the mortality among patients who received type-specific serum in addition to sulfadiazine was slightly higher than among those who were treated with the drug alone. This greater mortality is accounted for by the deliberate choice of the more severely ill patients for combination therapy and by the elimination from combined therapy of the least severely ill patients by their prompt response to chemotherapy alone. In our series 20 per cent of the patients treated with serum and sulfadiazine were selected because of bacteremia, detection of specific soluble substance in the blood or failure to respond to sulfadiazine alone. The remainder were unselected, and alternate patients were given serum. Comparison of the two groups reveals that the incidence of blood cultures positive for pneumococci was twice as great in the group undergoing combination therapy as in the other. The presence of circulating capsular carbohydrate was about three times as frequent in the former group as in the latter. (This difference approaches statistical significance—R. D. E. = 1.8.) There was a greater proportion of patients with infection due to type III pneumococci, which has a high mortality rate, in the group given both sulfadiazine and serum. The distribution as to age and day of illness on which therapy was begun was approximately the same in both groups. On the other hand, there were more deaths within twenty-four hours after admission in the sulfadiazine-treated group. The patients who received both therapeutic agents were undoubtedly more severely ill. The slightly higher mortality is explained by this definite difference in severity; the mortality in the group given both agents might have been higher if serum had not been given. We agree with other investigators [12] that there are a number of severely ill patients for whom serum is life saving. Final judgment as to the absolute value of this therapeutic agent must await results obtained from studies

11 Billings, F. T., Jr., and Wood, W. B., Jr.: Studies on Sulfadiazine: The Use of Sulfadiazine in the Treatment of Pneumococcal Pneumonia, Bull. Johns Hopkins Hosp. **69**:314, 1941.

12. Footnote 10 *a*, *b* and *c*.

of comparable patients. All the factors which are known to influence prognosis, such as age, duration of illness, bacteremia, detection of capsular polysaccharide and concurrent disease, must be taken into consideration.

The toxic manifestations associated with sulfadiazine were both less frequent and less severe than those encountered with sulfapyridine. Rarely was it found necessary to discontinue its administration. The more serious reactions, such as anemia, obstruction of the urinary tract [13] and granulocytopenia, were not observed in this series.

SUMMARY AND CONCLUSIONS

Two hundred and thirty-two patients with pneumococcic pneumonia were treated with sulfadiazine, and 70 received type-specific rabbit antipneumococcus serum in addition to the drug.

The gross mortality was 13.4 per cent in the former group and 14.3 per cent in the latter.

Those patients over 40 years of age treated late in the course of their illness were most numerous in both groups and had the highest mortality.

Fifty-eight and seven-tenths per cent of the drug-treated patients and 43 per cent of those in the other group had normal temperatures within forty-eight hours after the institution of therapy.

In the sulfadiazine-treated group two thirds of the patients who recovered received between 10 and 24 Gm. of the drug; two thirds of the patients had blood concentrations of free drug ranging from 5 to 10 mg. per hundred cubic centimeters.

Chemotherapy was discontinued after the temperature had been normal for eighteen to twenty-four hours. The temperatures of 83 per cent of the patients in the sulfadiazine-treated group who recovered remained normal after chemotherapy had been stopped. The remaining 17 per cent had a rise in temperature which was mild and of short duration in most instances.

Sulfadiazine is as effective as sulfapyridine in the treatment of pneumococcic pneumonias.

The mortality among patients who received both serum and sulfadiazine was slightly higher than that among the sulfadiazine-treated patients, but the former group was composed of more severely ill patients.

888 Montgomery Street, Brooklyn.

400 Fifty-Eighth Street, New York.

13. Since the preparation of this paper, numerous reports have appeared concerning renal damage—transitory and fatal—caused by sulfadiazine. We have since seen patients with hematuria and with oliguria, 1 of whom, severely stricken, died. This problem is under investigation in our service.

ACUTE BRUCELLOSIS

CLINICAL, BACTERIOLOGIC AND SEROLOGIC STUDIES OF THREE PATIENTS

BOWMAN WISE, M.D.
DURHAM, N. C.

Perusal of the large number of case reports of undulant fever contained in the literature is unsatisfactory not only because of frequent justifiable doubt as to the correctness of the diagnosis but because of the paucity of bacteriologic and serologic studies. Recently 3 patients suffering from undulant fever have afforded an excellent opportunity for study of the persistence of bacteremia and the behavior of demonstrable serum antibodies for Brucella throughout the course of the illness. The technics used for blood cultures and for the serologic tests have been described elsewhere.[1] All 3 patients came under observation during the first month of illness, and all received treatment with sulfonamide drugs, the results of which will be discussed.

REPORT OF CASES

CASE 1.—C. M., a 35 year old white man, a salesman, entered the hospital on Jan. 13, 1941, complaining of chills and fever of three weeks' duration. The familial, marital and past histories were irrelevant. He had frequently drunk unpasteurized milk.

The patient's illness began about Dec. 15, 1940 with malaise, fever, headache and mild pain in the upper part of the abdomen. At the onset he remained in bed for five days having daily chills and fever, but he felt sufficiently well to return to work on December 20. Three days later he again had fever and chills; these lasted three days and were followed by a relatively symptom-free interval of three days, after which daily fever, with the temperature reaching 40 C. (104 F.), and irregular chills became established. During the first two weeks of his illness he was given quinine, without improvement. On Jan. 6, 1941 he was admitted to another hospital. Physical examination revealed his liver to be palpable 2 cm. below the costal margin; splenic dulness to percussion was increased, but the spleen was not palpable. The hemoglobin content was 98 per cent and the white blood cell count 6,500, with polymorphonuclear leukocytes 42 per cent and small lymphocytes 58 per cent. Blood smears were positive for tertian malaria, and he was given quinine sulfate in doses up to 2 Gm. daily, without improvement. His temperature rose daily to 38 and 40 C. (100.4 to 104 F.). Repeated blood smears were negative for malarial parasites. Blood serum sent to the state laboratory was reported to give a positive agglutination reaction for undulant fever, and the patient was referred to Duke Hospital.

On admission the temperature was 38.7 C. (101.7 F.), the pulse rate 94, the respiratory rate 18 and the blood pressure 110 systolic and 60 diastolic. The patient appeared acutely ill. The pharynx was reddened. The heart and lungs were not remarkable. There was no abdominal tenderness. The edge of the liver was barely palpable; the spleen was felt 3 cm. below the costal margin. The remainder of the physical examination revealed nothing remarkable.

The Wassermann and Kahn reactions of the blood were negative. The hemoglobin content was 95 per cent; the red blood cells numbered 4,500,000 and the white blood cells 8,000, with polymorphonuclear leukocytes 51 per cent (stab forms 23 per cent), eosinophils 0, basophils 0, large lymphocytes 0, small lymphocytes 43 per cent, early lymphocytes 4 per cent and monocytes 2 per cent. The urine and stools were normal. Brucella suis was isolated from the blood, and the serum agglutinated brucella organisms through titers to 1:2,560. Subsequent cultural and serologic studies are summarized in chart 1.

During the first three days of the patient's stay in the hospital his temperature varied between 38.5 and 40.4 C. (101.3 and 104.7 F.). On the third day the administration of sulfathiazole was started in daily doses of 6 Gm. There was a gradual fall in temperature during the first week of drug therapy, at which time the patient complained for several days of severe pain in his heels, without objective findings. At the time of discharge from the hospital, on February 1, the patient was afebrile and symptom free, and the spleen was no longer palpable.

From the Departments of Medicine and Bacteriology, Duke University School of Medicine.

The patient returned for examination on February 25 and on March 25, having felt well during the intervals. Physical examination showed nothing remarkable. Cultures of blood taken on these visits were positive for Br. suis. He returned on April 25, complaining of dull aching pain in the lower thoracic portion of the spine of five days' duration. This pain was relieved by local application of heat and was greatly increased by attempts to lift anything. Examination revealed no tenderness over the vertebral spinous processes and no pain on motion of the spine. Roentgenograms of the spine were normal. Admission to the hospital was advised but refused.

The patient returned home and experienced marked increase in the pain in his back, requiring morphine for relief. A slight daily elevation of temperature was noted. He reentered the hospital on May 2.

The temperature was 38.5 C. (101.3 F.), pulse rate 84, respiratory rate 16 and blood pressure 128 systolic and 70 diastolic. The patient appeared ill and in great pain. There were point tenderness over the twelfth thoracic vertebra and severe pain on motion of the spine and lower parts of the legs. The results of the remainder of the physical examination were not remarkable.

The hemoglobin content was 114 per cent; the red blood cells numbered 5,520,000 and the white blood cells 4,850, with polymorphonuclear leukocytes 54 per cent, eosinophils 0, basophils 0, large lymphocytes 10 per cent, small lymphocytes 28 per cent, early lymphocytes 2 per cent

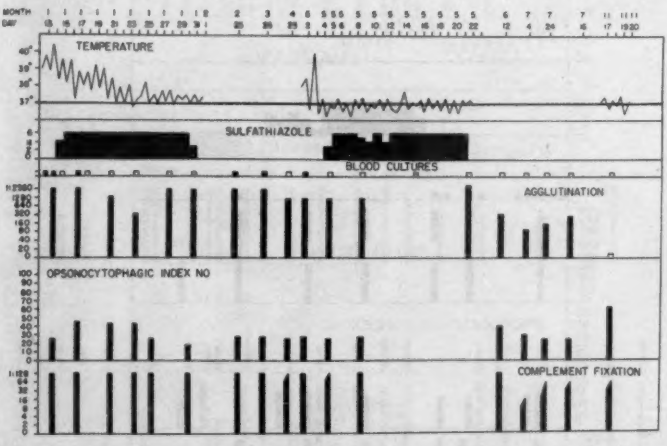


Chart 1 (case 1).—Bacteriologic and serologic observations. The filled-in spaces indicate positive and the blank spaces negative results. The sulfathiazole is expressed in grams.

and monocytes 6 per cent. The urine and stools were normal. Br. suis was isolated from blood taken on the day of admission. Other bacteriologic and serologic observations are given in chart 1. Roentgenograms of the spine showed no definite changes.

The patient's temperature fell promptly to a normal level, and after application of a plaster body jacket the pain in his back gradually improved. Administration of sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole) in daily doses of 6 Gm. was started four days after admission and continued throughout his stay in the hospital. He was greatly improved at the time of discharge, on May 23.

The patient was seen at intervals during the succeeding three months and complained only of occasional pain in the back. Repeated roentgenograms of his spine failed to show any definite lesion. Blood cultures were negative. He returned to the hospital on November 17, complaining of a "cold" of one week's duration. Chilliness and fever, with a temperature to 38.8 C. (101.8 F.), had been noted five days before admission. Although all symptoms of rhinitis and pharyngitis had abated by the time of his visit, he was admitted to the hospital for observation.

The temperature was 37.2 C. (100 F.), pulse rate 80, respiratory rate 20 and blood pressure 130 systolic and 70 diastolic. The results of physical examination were not remarkable. The hemoglobin content was 109 per cent; the red blood cells numbered 5,150,000 and the white blood cells 5,880, with polymorphonuclear leukocytes 38 per cent (stab forms 8 per cent), eosinophils 1 per cent, basophils 0, large lymphocytes 34 per cent, small lympho-

cytes 23 per cent and monocytes 4 per cent. Roentgenograms of the spine showed no osseous lesion. A blood culture was negative.

The patient was entirely afebrile and asymptomatic during his five day stay in the hospital. He was discharged on November 21. He has reported from time to time that he feels perfectly well and has had no recurrence of any symptoms.

CASE 2.—R. L., a 29 year old white man, a farmer, entered the hospital on March 24, 1941, complaining of abdominal pain of six weeks' duration. The familial, marital and past histories were not remarkable. On Dec. 23, 1940, while dressing the carcass of a pig which had aborted five times during the preceding year and was said to have had Bang's disease, the patient cut his hand and contaminated the wound with the animal's blood. On December 29 he cut his wrist and contaminated the wound with the blood of a steer from a herd known to be infected with the so-called contagious abortion disease.

The patient's illness began early in February 1941 with a gradual onset of malaise and increasing fatigability, soon followed by evening fever. During the first week of illness, while chopping wood, he was suddenly seized with knifelike epigastric pain, increased by

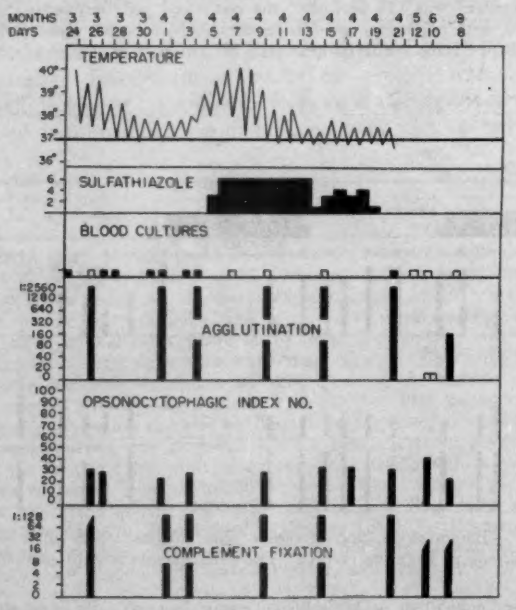


Chart 2 (case 2).—Bacteriologic and serologic observations. The filled-in spaces indicate positive and the blank spaces negative results. The sulfathiazole is expressed in grams.

inspiration and occasionally radiating to the back. This pain was not incapacitating but persisted for nearly two weeks, when it became a dull ache and lost all relation to inspiration. On February 10 he consulted a physician because of this abdominal pain, at which time his temperature was found to be 39.4 C. (102.9 F.). Fever, with the temperature reaching 38.3 to 40 C. (100.9 to 104 F.) daily, continued up to the time of entry to the hospital, along with increasing weakness and occasional night sweats. Four days before entry to the hospital he was given tablets of unknown nature, which caused nausea and vomiting, and their use was discontinued after twenty-four hours.

The patient was fairly well nourished and did not appear acutely ill. His temperature was 40 C. (104 F.), pulse rate 100, respiratory rate 18 and blood pressure 120 systolic and 80 diastolic. The skin was hot and dry. There was slight enlargement of the superficial lymph nodes. The tonsils were moderately hyperemic. The heart and lungs were not remarkable. There was no abdominal tenderness. The liver was not palpable; the spleen was felt 5 cm. below the costal margin on deep inspiration. The remainder of the examination was noncontributory.

The Wassermann and Kahn reactions of the blood were negative; the hemoglobin content of the blood was 78 per cent; the red blood cells numbered 4,620,000 and the white blood cells 5,800, with polymorphonuclear leukocytes 55 per cent (stab forms 6 per cent and juvenile cells 3 per cent), eosinophils 1 per cent, basophils 0, large lymphocytes 19 per cent, small lymphocytes 28 per cent and monocytes 1 per cent. Examinations and cultures of the urine and stools gave negative results. Br. suis was isolated from the blood, and serum agglutinins for brucella were present in a titer of 1:2,560. Subsequent bacteriologic and serologic observations are given in chart 2.

On the patient's admission to the hospital his abdominal pain promptly disappeared. On the fourth day in the hospital the temperature, which had risen daily to 39.5 C. (103.1 F.), fell to 38.5 C. (101.3 F.) and it did not rise above 37.9 C. (100.2 F.) during the succeeding week, for which reason sulfonamide drugs were not given. However, the temperature again rose daily to 40 C. (104 F.); so the administration of sulfathiazole was started in daily doses of 6 Gm. During the subsequent week there was a gradual fall of the temperature to normal. The daily dose of sulfathiazole was decreased to 5 Gm. during the week preceding discharge. At the time of discharge, on April 21, the patient was entirely afebrile and symptom free, but his spleen was still palpable. A culture of blood taken on this day was positive for Br. suis.

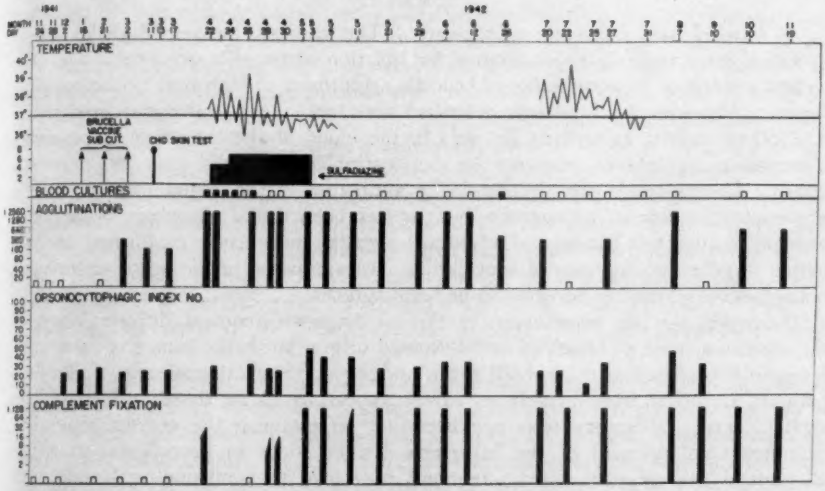


Chart 3 (case 3).—Bacteriologic and serologic observations. The filled-in spaces indicate positive and the blank spaces negative results. The sulfathiazole is expressed in grams.

He returned for examination on May 12, saying that he felt perfectly well and that he had gained 13 pounds (5.9 Kg.). The results of physical examination were entirely negative, the spleen being no longer palpable. Cultures of blood taken on this and subsequent visits were negative. He returned again on June 9, having continued to be in excellent health and having gained an additional 10 pounds (4.5 Kg.). He was last seen on September 8, at which time he was discharged from observation.

CASE 3.—D. S., a 25 year old man, a technician employed in the brucellosis laboratory, was admitted to the hospital on April 22, 1942, complaining of general malaise. The past history was noncontributory. In March 1941 he was given three subcutaneous injections of a brucella vaccine at weekly intervals.

At the time of admission his temperature was 37.2 C. (99 F.), pulse rate 92, respiratory rate 20 and blood pressure 120 systolic and 70 diastolic. There was slight enlargement of the superficial lymph nodes, but the remainder of the examination gave negative results.

The Kahn and Kline reactions were negative. The hemoglobin content was 103 per cent; the red blood cells numbered 5,270,000 and the white blood cells 4,800 with polymorphonuclear leukocytes 70 per cent (stab forms 6 per cent), eosinophils 0, basophils 0, large lymphocytes 1 per cent, small lymphocytes 24 per cent and monocytes 5 per cent. The urine was normal. Serum agglutinins and complement-fixing antibodies for Brucella were present in high titers,

and Br. suis was isolated from the blood taken on admission. Subsequent bacteriologic and serologic observations are given in chart 3.

The patient was given sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) in daily doses of 6 Gm. His temperature gradually fell to normal, and he was discharged from the hospital on May 6, 1942. He was followed closely and, except for having an infection of the upper respiratory tract, remained well until July 15, when malaise again developed with arthralgia and fever. A culture of blood taken on June 26 was positive for Br. suis. He was readmitted to the hospital on July 20.

On admission his temperature was 38.2 C. (100.8 F.), pulse rate 100 and respiratory rate 24. The results of physical examination were not remarkable. The hemoglobin content was 84 per cent; the red blood cells numbered 4,260,000 and the white blood cells 6,900 with polymorphonuclear leukocytes 42 per cent (stab forms 6 per cent), eosinophils 0, basophils 0, large lymphocytes 0, small lymphocytes 44 per cent, early lymphocytes 1 per cent and monocytes 13 per cent. The urine was normal. A roentgenogram of the chest was normal. Further bacteriologic and serologic observations are given in chart 3.

The patient's treatment was entirely symptomatic. His fever gradually subsided, and he was discharged from the hospital on July 31. Since this time he has been followed closely and has remained well.

COMMENT

1. Clinical and Laboratory Diagnosis.—The clinically suspected diagnosis of undulant fever requires substantiation by isolation of brucella organisms from the patient's blood or demonstration of brucella agglutinins in high titer in the patient's serum. Although the 3 patients described here had serum agglutinins in titers of 1:2560 or higher, as well as Br. suis in the blood at the time they came under observation, agglutinins may not be demonstrable for weeks after the onset of illness. Demonstrable complement-fixing antibodies in the serum usually parallel agglutinins in time of appearance, but, as has been stated elsewhere,[1e] the complement fixation test has no real advantage over the more easily performed agglutination test for the diagnosis of brucellosis. Determination of the opsonocytophagic index has been found to be of no value for diagnosis.

According to our experience the clinical diagnosis requires differentiation of the condition from all fevers of undetermined origin, but brucellosis has been most frequently confused with typhoid fever and infectious mononucleosis. Although patients suffering from brucellosis rarely appear as ill as those suffering from typhoid fever, laboratory tests are necessary to establish the correct diagnosis. Significant enlargement of the superficial lymph nodes in brucellosis, to which Bloomfield has recently called attention,[2] may lead to confusion with infectious mononucleosis. Furthermore, the differential white cell count of patients suffering from acute brucellosis frequently reveals abnormal lymphocytes suggestive of the early stage of infectious mononucleosis.

2. Fever, Bacteremia and Duration of Illness.—The 3 patients discussed here were febrile at the time they came under observation, and blood cultures were positive for Br. suis. Febrile episodes lasted usually seven to ten days. The well known undulating type of fever in this disease is illustrated in chart 2 (case 2). The duration of the illness varied. Recovery from the initial episode of fever was apparently complete, and in the intervals between febrile episodes the patients were symptom free, despite the fact that bacteremia was demonstrated by recovery

1. (*a*) Wise, B., and Kerby, G. P.: Cultivation of Brucella from the Blood, to be published. (*b*) Wise, B.: An Evaluation of the Brucella Opsonocytophagic Test, Am. J. M. Sc. **200**:520-523 (Oct.) 1940. (*c*) Jersild, M.: A Cytophagic Reaction Employed in the Diagnosis of Brucella Infection, J. Infect. Dis. **68**:16-19 (Jan.) 1941. (*d*) Foshay, L., and LeBlanc, T. J.: The Derivation of an Index Number for the Opsonocytophagic Test, J. Lab. & Clin. Med. **22**:1297-1300 (Sept.) 1937. (*e*) Wise, B., and Craig, H. W.: The Brucella Complement-Fixation Reaction, J. Infect. Dis. **70**:147-151 (March-April) 1942.

2. Bloomfield, A. L.: Enlargement of the Superficial Lymph Nodes in Brucella Infection, Am. Rev. Tuberc. **45**:741-750 (June) 1942.

of the organism from the blood. It is not generally recognized that positive blood cultures may be obtained long after complete recovery from the acute illness or even in the absence of a frank history of illness.[3] In cases 1 and 3 recurrence of bacteremia, shown by positive blood cultures, preceded recurrence of fever, but bacteremia without any return of fever or symptoms occurred in case 2. Such possibilities should be kept in mind in all cases of brucellosis and should serve as a caution against interpretation of a single positive blood culture as indicating clinical disease.

3. Sulfonamide Therapy.—In a review of the use of sulfonamide drugs in the treatment of undulant fever, Blumgart and Gilligan[4] in 1939 concluded that sulfanilamide is a valuable therapeutic agent. They stated: "The findings, following sulfanilamide treatment, of diminished agglutination titers and of negative blood cultures in cases which had shown positive cultures before treatment, bear further evidence that the infection is controlled." Recent in vitro experiments have shown sulfathiazole and sulfadiazine to have an almost equal bacteriostatic action on Br. suis and one considerably more pronounced than that of sulfanilamide.[5] In the 3 cases reported sulfathiazole or sulfadiazine was given with little or no apparent benefit. Possibly the drugs had some effect in reducing the bacteremia, but subsequent positive blood cultures were obtained in all cases, even as early as several days after administration of the drug was discontinued. It seems likely that the number of positive blood cultures obtained in cases of undulant fever, both during and after the febrile illness, depends primarily on the number of cultures made and also on the cultural technic employed. It is of particular interest to compare the persistence of bacteremia in the case reported by Keefer[3a] in 1924, in which no specific treatment was given with that in the 3 instances reported here. Regardless of whether sulfonamide drugs are considered to have some beneficial effect in sterilizing the blood during the initial febrile episode, or possibly shortening the course of the illness, the use of these drugs has failed to prevent relapse.

4. Serologic Reactions: Persistence of Serum Antibodies.—No significant changes in titers of brucella agglutinin or complement-fixing antibodies were observed after sulfonamide therapy in the cases reported. When agglutination and complement fixation tests are carried out at frequent intervals, considerable variations in titers may be observed over a period of days regardless of whether or not chemotherapy is used. A relatively prompt disappearance of demonstrable serum agglutinins usually follows complete recovery, but complement-fixing antibodies, as is well known, may persist for months. The results of determinations of the opsonocytophagic index have been so variable as to preclude discussion. This experience is in complete agreement with that of Castaneda, Tovar Mancera and Velez.[6]

3. (*a*) Keefer, C. S.: Report of a Case of Malta Fever Originating in Baltimore, Maryland, Bull. Johns Hopkins Hosp. **35**:6-14 (Jan.) 1924. (*b*) Shaw, E. A.: II. The Ambulatory Type of Case in Mediterranean or Malta Fever, Mediterranean Fever Reports, London, 1907, pt. 4, pp. 8-15.

4. Blumgart, H. L., and Gilligan, D. R.: The Treatment of Undulant Fever with Sulfanilamide and Related Compounds, M. Clin. North America **23**:1193-1203 (Sept.) 1939.

5. (*a*) Kempner, W.; Wise, B., and Schlayer, C.: Manometric Determination of the Effects of Various Sulfanilamide Compounds on Brucella Melitensis, Am. J. M. Sc. **200**:484-492 (Oct.) 1940. (*b*) Wise, B.: In Vitro Studies of Sulfonamide Action on Organisms of the Brucella Group and the Counteracting Effect of Para-Aminobenzoic Acid, J. Pharmacol. & Exper. Therap. **76**:156-160 (Oct.) 1942.

6. Castaneda, M. R.; Tovar Mancera, R., and Velez, R.: Studies on Brucellosis in Mexico: Comparative Study of Various Diagnostic Tests and Classification of the Isolated Bacteria, J. Infect. Dis. **70**:97-102 (March-April) 1942.

5. Complications and Sequelae.—Neither complications nor sequelae were observed in cases 2 and 3. Although osteitis, a fairly common complication of undulant fever,[7] was strongly suspected in case 1, no lesion was ever satisfactorily demonstrated by roentgenologic examination.

SUMMARY

1. The clinical histories and bacteriologic and serologic observations in 3 cases of undulant fever are presented and discussed.

2. Emphasis is placed on the persistence and recurrence of bacteremia, which may be detected in symptom-free intervals between febrile episodes as well as after complete recovery.

3. The behavior of demonstrable serum agglutinins and complement-fixing antibodies during and after the period of illness is illustrated.

4. It is noted that the therapeutic effect of sulfathiazole or sulfadiazine in these cases was not striking.

Box 3703, Duke University.

7. Bishop, W. A.: Vertebral Lesions in Undulant Fever, J. Bone & Joint Surg. **21**:665-763 (July) 1939.

ALTERATIONS IN BIOLOGIC OXIDATION IN THYROTOXICOSIS

I. THIAMINE METABOLISM

ROBERT H. WILLIAMS, M.D.

ENRIQUE EGANA, M.D.*

PAUL ROBINSON, A.B.

SAMUEL P. ASPER, M.D.

AND

CHARLES DUTOIT, M.D.

BOSTON

A great deal of evidence has accumulated to indicate that the thyroid gland is a part of an integrated system which regulates biologic oxidations. The nervous system, the pituitary gland and the cells and fluids of the body are other important entities in this system (chart 1). Disturbance in any one of these units may affect the functions of the others. For example, removal of the pituitary gland results in decreased function of the thyroid gland, the body cells and the nervous system. Removal of the thyroid leads to increased production of the thyrotropic hormone and to decreased activity of the body cells and the nervous system. Conversely, with thyrotoxicosis or the feeding of thyroid there is stimulation of the nervous system and the metabolism of the body cells. Alterations in biologic oxidations of the cells have been demonstrated to exert an effect on the segments of the system shown in chart 1; however, little consideration has been given to the concept that certain abnormalities in the functions of the body cells might lead to the development of thyrotoxicosis.

Webster and Chesney [1] have found that in rabbits fed a diet consisting chiefly of cabbage goiter of a hyperplastic type developed and the metabolic rate was lowered. However, within a few days after iodine was given to these goitrous animals, they exhibited signs of thyrotoxicity and a marked elevation of the metabolic rate. When iodine was given at the beginning of the cabbage diet it offered complete protection against the goitrogenic effects of cabbage.[2] Marine, Baumann, Spence and Cipra [3] demonstrated that a cabbage diet induces goiter because the cyanide it contains inhibits the consumption of oxygen. Rabbits fed methyl cyanide had the same type of goiter.[4] Moreover, the simultaneous administration of iodine tended to prevent the goitrogenic effects of the cyanide.

From the Thorndike Memorial Laboratory, Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School.

*Fellow (Chile) of the Rockefeller Foundation 1941-1942. Dr. Egana did not read this manuscript because of difficulties in getting it transported to Chile.

1. Webster, B., and Chesney, A. M.: Endemic Goiter in Rabbits: III. Effect of Administration of Iodine, Bull. Johns Hopkins Hosp. **43**:291, 1928.

2. Webster, B., and Chesney, A. M.: Studies in the Etiology of Simple Goiter, Am. J. Path. **6**:275, 1930.

3. Marine, D.; Baumann, E. J.; Spence, A. W., and Cipra, A.: Further Studies on Etiology of Goiter with Particular Reference to the Action of Cyanides, Proc. Soc. Exper. Biol. & Med. **29**:772, 1932.

4. Marine, D.; Rosen, S. H., and Cipra, A.: Further Studies on the Exophthalmos in Rabbits Produced by Methyl Cyanide, Proc. Soc. Exper. Biol. & Med. **30**:649, 1933.

Uotila [5] found that rats continuously exposed to cold had an increase in the thyrotropic function and marked hyperplasia of the thyroid cells. However, if the pituitary stalk was sectioned before the animal was subjected to the cold, such changes were not found. These observations emphasize the interrelation of the various segments of the system presented in chart 1.

Means, Hertz and Lerman [6] noted that hyperthyroidism developed in some patients while they were following a strenuous regimen for the reduction of weight. We have seen this phenomenon sufficiently often to suspect that certain dietary restrictions may lead to the development of thyrotoxicosis. It is of interest that various deficiencies of vitamins, as well as of other substances, have been said to promote the development of goiter. Spence [7] observed the development of simple goiter in 15 of 20 rats kept on a diet deficient in vitamins A, B, C and D. Sandberg and Holly [8] reported that in rabbits kept on a diet deficient in vitamin B_1 hyperplasia of the thyroid developed but that administration of vitamin B_1 to these animals with goiter caused only slight change in the anatomic state of the gland. However, Fischer [9] found not only that vitamin B_1 plays a contributory part in the production of endemic goiter but that the feeding of this vitamin in unpolished

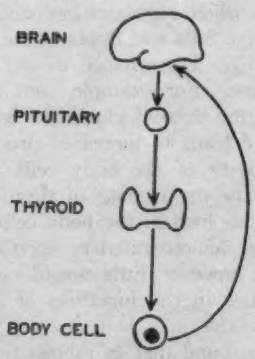


Chart 1.—An integrative system concerned with biologic oxidations.

rice produces the same histologic effect on the thyroid gland as the feeding of iodized salt. On the other hand, Carpenter and Sharpless [10] concluded that vitamin B deficiency alone does not affect the size, structure or iodine content of the thyroid gland of the rat.

Thus, one can see that the cellular oxidations have distinct influences on the thyroid gland, but further study is necessary to establish the precise nature and extent of these relationships.

5. Uotila, N. N.: Role of Pituitary Stalk in Regulation of Thyrotropic and Thyroid Activity, Proc. Soc. Exper. Biol. & Med. **41**:106, 1939.

6. Means, J. H.; Hertz, S., and Lerman, J.: Nutritional Factors in Graves' Disease, Ann. Int. Med. **11**:429, 1937.

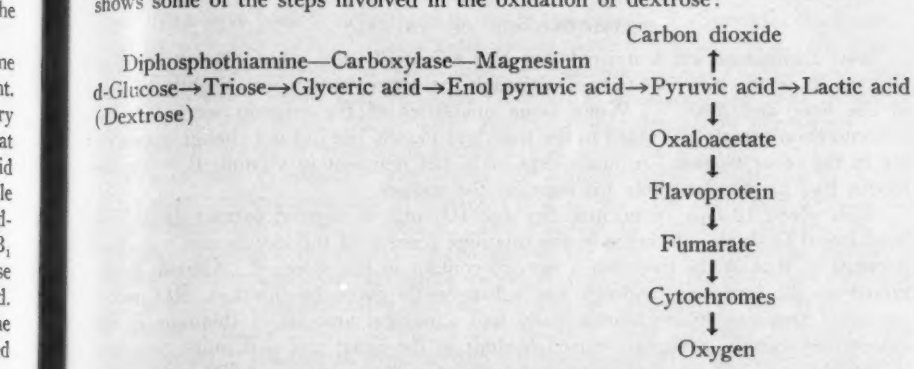
7. Spence, A. W.: The Effect of Vitamin Deficiency on the Structure of the Thyroid and Thymus Glands, Brit. J. Exper. Path. **13**:157, 1932.

8. Sandberg, M., and Holly, O. M.: On the Influence of Vitamin B and of Iodine on the Calcium and Phosphorus Metabolism of Rabbits with Hyperplastic Thyroids, J. Biol. Chem. **99**:547, 1933.

9. Fischer, E.: Production and Prevention of Goiter in Rat Experiments, Nutrition Abstr. & Rev. **3**:827, 1934.

10. Carpenter, M. D., and Sharpless, G. R.: A Study of the Effect of Vitamin B and Iodine on the Weight, Iodine Content and Structure of the Thyroid Gland of the Rat, J. Nutrition **13**:235, 1937.

At the Thorndike Memorial Laboratory we have been investigating in thyrotoxic patients the nature of the reactions of the various segments of the system of biologic oxidations, as presented by von Szent-Györgyi.[11] The following outline shows some of the steps involved in the oxidation of dextrose:



In this report we are concerned chiefly with the interrelationship of the thyroid and thiamine functions, particularly the effects of the former on the latter. First, however, we wish to mention some of the physiologic reactions of this vitamin.

The biologically active form of thiamine is cocarboxylase, or diphosphothiamine.[12] Although the phosphorylation of thiamine occurs in all nucleated cells, the liver and kidneys are particularly active in this process. Almost all the thiamine found in the cells is in the phosphorylated form, whereas essentially all the thiamine in the plasma and urine is in the free form. Diphosphothiamine is primarily concerned with the decarboxylation of alpha ketonic acids, particularly pyruvic acid.[13] In this capacity it is part of a protein-diphosphothiamine-magnesium compound in which the three components are present in the ratio of 1 : 1 : 5 or 1 : 1 : 7.

Diphosphothiamine is necessary for the transfer of phosphorus from phospho-(enol)-pyruvic acid to adenylic acid, and, since pyruvate oxidations cause the storage of a considerable amount of energy as adenosine triphosphate, diphosphothiamine is indirectly involved in the synthesis of glycogen from d-glucose (dextrose). Diphosphothiamine is also necessary in the synthesis of fatty acids from carbohydrates; this action is probably secondary to its effect on pyruvate metabolism.

It may thus be noted that not only thyroid but diphosphothiamine is intimately concerned with cellular oxidation. Since it has been shown by Plimmer,[14] Cowgill and associates[15] and others[16] that the requirements of vitamin B are propor-

11. von Szent-Györgyi, A.: On Oxidation, Fermentation, Vitamins, Health and Disease, Baltimore, Williams & Wilkins Company, 1939.

12. Ochoa, S.: Cocarboxylase, in Symposium on Vitamins Held at the University of Chicago, Sept. 15-17, 1941, Chicago, University of Chicago Press, 1942.

13. Banga, I.; Ochoa, S., and Peters, R. A.: Pyruvate Oxidation in Brain: VI. The Active Form of Vitamin B_1 and the Role of C_4 Dicarboxylic Acids, Biochem. J. **33**:1109, 1939.

14. Plimmer, R. H. A.: Vitamins, Brit. M. J. **1**:239, 1926. Plimmer, R. H. A.; Rosedale, J. L., and Raymond, N. H.: Experiments on Nutrition: VI. Balance of Food by Vitamin B, Biochem. J. **21**:913, 1927.

15. (*a*) Cowgill, G. R., and Palmieri, M. L.: Studies in the Physiology of Vitamins: XXII. The Effect of Experimentally Induced Hyperthyroidism on the Vitamin B Requirement

(Footnotes continued on next page)

tional to the amount of food metabolized, one might expect to find disturbances in thiamine metabolism in thyrotoxicosis. Many studies have been made of this subject with animals, but studies of patients are somewhat incomplete.

THYROTOXICOSIS OF ANIMALS

Rats maintained on a normal diet had essentially the same concentration of vitamin B_1 in the different tissues, although the concentration was slightly greater in the liver and heart.[17] When large quantities of the vitamin were fed, the concentration greatly increased in the liver and muscle but did not change appreciably in the other tissues. Animals kept on a diet deficient in vitamin B_1[18] for one month had no demonstrable thiamine in the tissues.

Rats given 12 Gm. of normal diet and 100 mg. of thyroid extract daily have been found to show a decrease in the thiamine content of the kidney and a marked decrease in that of the liver but a normal content in the spleen.[19] Animals maintained on the foregoing regimen and subsequently given by injection 500 micrograms of thiamine hydrochloride daily had a normal amount of thiamine in the spleen and muscle, a slightly raised content in the heart and a definite reduction in the liver and kidney when compared with normal rats receiving 500 micrograms of thiamine hydrochloride daily. The hyperthyroid rats receiving the thiamine eliminated the same amount of vitamin B_1 in the urine as did the normal rats given the same amount of thiamine. This suggests that the increased metabolism produced by the thyroid feeding did not increase the amount of vitamin B_1 destroyed by the body metabolism.

Peters and Rossiter[20] demonstrated that the cocarboxylase content of boiled tissue extracts from the hyperthyroid animals which they studied was intermediate in value between that from normal animals and that from animals showing symptoms of vitamin B_1 deficiency. The injection of thiamine hydrochloride increased the diphosphothiamine content of the tissues of both normal and hyperthyroid animals.

Dogs kept on a diet deficient in vitamin B and fed large doses of desiccated thyroid had anorexia and lost weight much sooner than dogs on the same diet without thyroid.[21] The administration of large doses of thiamine to these animals caused a marked increase in appetite and a gain in weight,[22] beginning within forty-eight hours.[23] Furthermore, dogs kept on a diet well supplemented with

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of Pigeons, Am. J. Physiol. **105**:146, 1933. (*b*) Himwich, H. E.; Goldfarb, W., and Cowgill, G. R.: Studies in the Physiology of Vitamins: XVII. The Effect of Thyroid Administration upon the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, ibid. **99**:689, 1932.

16. Hendricks, W. A.: The Relation of Vitamin B Requirement to Metabolism, ibid. **105**: 678, 1933. Williams, R. R., and Spies, T. D.: Vitamin B_1 and Its Use in Medicine, New York, The Macmillan Company, 1938, chap. 20.

17. Brodie, J. B., and MacLeod, F. L.: Quantitative Experiments on the Occurrence of Vitamin B in Organs, J. Nutrition **10**:179, 1935. Leong, P. C.: Vitamin B_1 in the Animal Organism: I. The Maximum Storage of Vitamin B_1 in the Tissues of the Rat, Biochem. J. **31**:367, 1937.

18. The terms thiamine and vitamin B_1 are synonymous.

19. Drill, V. A.: The Effect of Experimental Hyperthyroidism on the Vitamin B_1 Content of Some Rat Tissues, Am. J. Physiol. **122**:486, 1938.

20. Peters, R. A., and Rossiter, R. J.: Thyroid and Vitamin B_1, Biochem. J. **33**:1140, 1939.

21. Cowgill, G. R.; Rosenberg, H. A., and Rogoff, J.: Studies in Physiology of Vitamins: Effect of Exercise on Time Required for Development of Anorexia Characteristic of Lack of Undifferentiated Vitamin B, Am. J. Physiol. **98**:589, 1931.

22. Himwich, H. E.; Goldfarb, W., and Cowgill, G. R.: The Vitamin B Complex in Relation to Food Intake During Hyperthyroidism, Proc. Soc. Exper. Biol. & Med. **28**:646, 1931.

23. Drill, V. A.: The Calorie Intake and Weight Balance of Hyperthyroid Dogs in Relation to Vitamin B_1 and Yeast, Am. J. Physiol. **132**:629, 1941.

vitamin B and fed thyroid did not tend to show anorexia or loss of weight. Yet, when very large doses of thyroid were given, the animals lost weight and died [24] in spite of the fact that the tissue content of vitamin B_1 can be maintained at a normal level by the injection of large quantities of thiamine.[19] Some of these phenomena have been demonstrated in rats [25] and pigeons.[26] Sure and Buchanan,[25] working with rats, showed that a much better protection against the toxic effects of thyroxin was afforded by yeast than by thiamine alone. Furthermore, Drill and Sherwood [27] found that although vitamin B_1 stimulated the food intake of hyperthyroid rats, it did not promote gain in weight, under the conditions used, until a rich source of vitamin B complex was added to the diet.

Frazier and Friedman [28] found that the administration of thyroid to guinea pigs caused marked depletion of glycogen in the liver; the same diet without the thyroid permitted a gain in weight. The addition of iodine or dextrose to the diet did not increase the amount of glycogen in the liver. However, the studies of Drill [29] demonstrated that rats which received large quantities of vitamins B_1 and G plus thyroxin maintained a normal quantity of glycogen in the liver.

Abelin, Knuchel and Spichtin [30] reported that large amounts of casein, egg yolk or yeast in the diet of hyperthyroid animals lowered the basal metabolic rate, prevented the depletion of glycogen stores of the liver and muscles and prevented hepatic injury. Moreover, Drill and Hays [31] demonstrated that in dogs fed large quantities of thyroid, yeast afforded a marked protection to the hepatic function, as measured by the bromsulphalein test.

Buell, Strauss and Andrus [32] found that in the gastrocnemius muscles of severely thyroxinized animals the formation of lactic acid was inhibited, as evidenced by a lower initial value, slower rate of formation and earlier cessation of production than those of the normal animal. They also found a decreased glycogen content of the muscle but did not believe this was the cause of the decrease in production of lactic acid. They suggested that in the thyroxinized animal there may be a decreased capacity for the synthesis of glycogen from lactic acid.

In summary, studies with animals have shown that with the administration of large doses of thyroid there is a demand for an increased supply of thiamine, which if not supplied results in a depletion of the body stores of this vitamin leading to anorexia, loss of weight, decreased stores of glycogen in the muscles and liver and decreased hepatic function. These changes can be largely reversed or prevented by the concomitant administration of vitamin B_1 and the vitamin B complex.

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24. Sure, B., and Smith, M. E.: Hyperthyroidism and Nutrition: I. Vitamin B and Thyroxine, J. Nutrition **7**:547, 1934.

25. Sure, B., and Buchanan, K. S.: Antithyrogenic Action of Crystalline Vitamin B, J. Nutrition **13**:513, 1937. Sure and Smith.[24]

26. (*a*) Cowgill, G. R., and Klotz, B. H.: Determination of the Vitamin B Requirement of the Pigeon and Its Bearing on the Theory of Vitamin B Function, Am. J. Physiol. **81**:470, 1927. (*b*) Cowgill and Palmieri.[15a] Cowgill, Rosenberg and Rogoff.[21]

27. Drill, V. A., and Sherwood, C. R.: The Effect of Vitamin B_1 and the Vitamin B_2 Complex on the Weight, Food Intake, and Estrus Cycle of Hyperthyroid Rats, Am. J. Physiol. **124**:683, 1938.

28. Frazier, W. D., and Friedman, H.: Alterations in Liver Glycogen Following Thyroid, Iodine and Glucose Feedings, Surg., Gynec. & Obst. **60**:27, 1935.

29. Drill, V. A.: The Effect of Yeast on the Liver Glycogen of White Rats During Hyperthyroidism, J. Nutrition **14**:355, 1937.

30. Abelin, I.; Knuchel, M., and Spichtin, W.: The Effect of Vitamins on the Course of Experimental Hyperthyroidism, Biochem. Ztschr. **228**:189, 1930.

31. Drill, V. A., and Hays, H. W.: Hyperthyroidism and Liver Function in Relation to B Vitamins, Proc. Soc. Exper. Biol. & Med. **43**:450, 1940.

32. Buell, M. V.; Strauss, M. B., and Andrus, E. C.: Metabolic Changes Involving Phosphorus and Carbohydrate in the Autolyzing Gastrocnemius and Cardiac Muscles of Normal, of Thyroxinized and of Adrenalectomized Animals, J. Biol. Chem. **98**:645, 1932.

THYROTOXICOSIS OF PATIENTS

Frazier and Ravdin,[33] as well as Means,[34] have pointed out that in patients with exophthalmic goiter there are often symptoms suggesting thiamine deficiency. One of us (R. H. W.) has been interested in this association for several years and has observed not infrequently the coexistence of hyperthyroidism, pellagra and ariboflavinosis. The tongue is sometimes fiery red and its papillae atrophic; hyperexia may be replaced by anorexia, and loss of weight becomes marked; achlorhydria, "dyspepsia," delayed emptying time of the stomach and diarrhea are fairly common. Tachycardia, cardiac dilatation, generalized edema, decrease in circulation time and vasomotor disturbances are also encountered. Decrease in strength and tolerance to exercise are almost always demonstrable.

Borson [35] found that the daily excretion of thiamine in the urine was below normal in most of a group of 8 thyrotoxic patients. He also found that the excretion of a test dose of thiamine was substandard in nearly each instance.

In order to secure further information as to the frequency of coexistence of thyrotoxicosis and thiamine deficiency, we determined the vitamin B content of the blood of 40 thyrotoxic subjects. The patients studied were scattered in seven hospitals in Boston and represented various social classes.[36] There was no selection

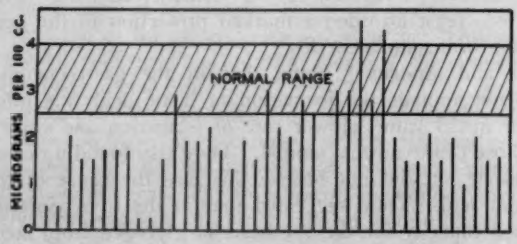

Chart 2.—Amount of free thiamine in the blood of 40 thyrotoxic patients.

other than that contingent on a basal metabolic rate above + 20 per cent and definite clinical evidence of thyrotoxicosis. Five patients had received a few small doses of thiamine, chiefly in the form of yeast. Blood was drawn from the patients when they were in a resting and fasting state. Whenever a tourniquet was used for a venipuncture, an interval of about five seconds was allowed to elapse between release of the tourniquet and withdrawal of blood. Enough blood was drawn at one time for determinations of thiamine, diphosphothiamine, pyruvic acid and lactic acid.

Thiamine.—Estimations of thiamine was performed by the thiochrome method of Jansen [37] modified by Egana and Robinson.[38] This method depends on the

33. Frazier, W. D., and Ravdin, I. S.: The Use of Vitamin B_1 in the Preoperative Preparation of the Hyperthyroid Patient, Surgery **4**:680, 1938.

34. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

35. Borson, H. J.: Clinical Application of the Thiochrome Reaction in the Study of Thiamin (Vitamin B_1) Deficiency, Ann. Int. Med. **14**:1, 1940.

36. Dr. Herbert Sise, of the Lahey Clinic, gave us the opportunity of studying many of these patients.

37. Jansen, B. C. P.: A Chemical Determination of Aneurin (Vitamin B_1) by the Thiochrome Method, Rec. d. trav. chim. d. Pays-Bas **55**:1046, 1936.

38. Egana, E., and Robinson, P. F.: The Estimation of Diphosphothiamin and Thiamin in Blood, to be published.

quantitative oxidation of thiamine to thiochrome, in the presence of alkaline ferricyanide, measurable by the intensity of blue fluorescence in ultraviolet light.

Of the 40 specimens of blood studied, 31 had a lower thiamine level than normal (chart 2). We found the range for 25 normal persons to be between 2.5 and 4 micrograms per hundred cubic centimeters.

Borson,[35] using thiamine saturation tests, found evidence of deficiency in all 12 thyrotoxic patients he tested.

Diphosphothiamine.—Since the biologically active form of thiamine is diphosphothiamine, we estimated the amount of the latter in each of the aforementioned specimens of blood. The method employed was one recently described by Egana and Robinson.[38] It depends on the quantitative conversion of diphosphothiamine to diphosphothiochrome, the latter giving a blue fluorescence in ultraviolet light. The intensity of the fluorescence is compared with that exhibited by a gradient set of standard solutions that have been carried through the same process as the unknown, and thereby the amount of diphosphothiamine estimated. A known amount of thiamine was added to almost every specimen of blood, and the percentage recoverable was determined. In some patients only a small amount

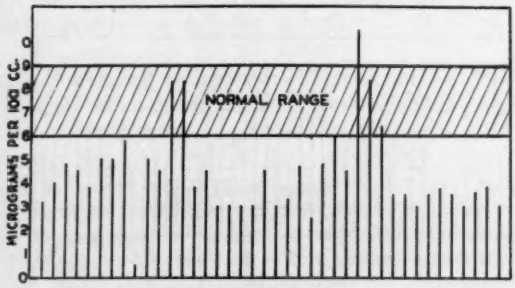

Chart 3.—Amount of diphosphothiamine in the blood of 40 thyrotoxic patients.

was recovered, but these patients tended to have a high pyruvic acid content in the blood. (This will be discussed later.) A few such patients were followed while receiving treatment with thiamine. As they became saturated with this vitamin and as the diphosphothiamine level of the blood returned to normal, the percentage of vitamin recovered by the technic described tended to return to normal.

The diphosphothiamine content of the blood of 25 normal persons in a resting and fasting state was found to be between 6 and 9 micrograms per hundred cubic centimeters. However, the amount of this substance was below the normal level in 34 of the 40 thyrotoxic patients examined (chart 3). Furthermore, in the majority of cases the reduction was moderate. The amount of free and of phosphorylated thiamine tended to parallel each other, although in a few instances there were distinct discrepancies. For example, the patients with diphosphothiamine levels, respectively, of 3 to 4, 4 to 5.5 and above 5.5 micrograms per hundred cubic centimeters had average thiamine levels of 1.1, 1.6 and 3 micrograms per hundred cubic centimeters. It was our impression that the determinations of diphosphothiamine were a little more accurate than those of thiamine. Furthermore, on following some patients from day to day, we did not observe quite as much fluctuation in the phosphorylated form.

When the thyrotoxic subjects were considered as a group, there was no correlation between the amount of vitamin B deficiency and the height of the basal metabolic rate or the duration of the disease. However, when the subjects were considered individually, these factors were significant, as was, of course, the food eaten.

Pyruvic Acid.—When the blood was collected for the thiamine determinations about 6 cc. was placed in a bottle with 0.2 cc. of 30 per cent sodium monoiodoacetate and 1 drop of 20 per cent potassium oxalate solution. The use of the iodoacetate was based on the experiments of Bueding and Wortis,[39] which showed that this substance would prevent the disappearance of pyruvic acid from the blood. These investigators also found that if blood to which sodium monoiodoacetate had been added was allowed to stand at room temperature for thirty minutes, an increase of pyruvic acid of 3 to 20 per cent was observed. On the other hand, if blood was precipitated at intervals ranging from forty seconds to ten minutes after withdrawal from the vein, significant losses were observed when the stabilizing medium was not used. Our observations confirm these principles; however, we did not notice significant changes in pyruvic acid if the blood was kept in the ice box for thirty minutes or more before precipitation.

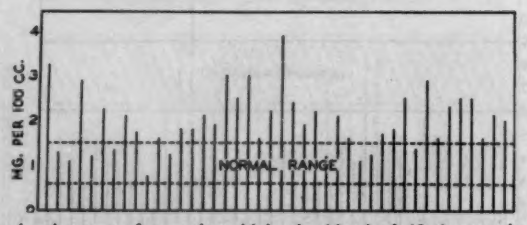

Chart 4.—Amount of pyruvic acid in the blood of 42 thyrotoxic patients.

We used the Lu [40] method for the determination of pyruvic acid with essentially the modifications described by Bueding and Wortis.[39] This method depends on the conversion of pyruvic acid into its hydrazone by the use of 2,4-dinitrophenylhydrazine, the extraction of this substance with ethyl acetate, the use of sodium carbonate for the separation of the pyruvate hydrazone from the excess hydrazine and the hydrazones of other ketones and aldehyde derivatives, and the quantitation in a photoelectric colorimeter of the red color produced by the addition of sodium hydroxide.

We have found that the level of pyruvic acid of the blood during fasting in most normal persons is between 0.5 and 1.5 mg. per hundred cubic centimeters and usually not below 1 mg.; rarely, it is slightly above 1.5 mg. This is in essential agreement with the results of Johnson.[41] However, our normal values are higher than the ones obtained by Lu [42] and slightly higher than the ones of Bueding and Wortis.[39]

39. Bueding, E., and Wortis, H.: The Stabilization and Determination of Pyruvic Acid in the Blood, J. Biol. Chem. **133**:585, 1940.

40. Lu, G. D.: XXX. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B_1 Deficient States: I. A Rapid, Specific and Sensitive Method for the Estimation of Blood Pyruvate, Biochem. J. **33**:249, 1939.

41. Johnson, R.: Personal communication to the authors.

42. Lu, G. D.: Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B_1 Deficient States: II. Blood Pyruvate Levels in the Rat, Pigeon, Rabbit and Man; III. The Relation of Blood Pyruvate to Cardiac Changes, Biochem. J. **33**:774, 1939.

The pyruvic acid content of the blood was elevated in 32 of 42 thyrotoxic patients whom we examined. Within a wide range, there was a definite correlation of this change with the amount of diphosphothiamine present. For example, all 21 patients with a diphosphothiamine level below 4 micrograms per hundred cubic centimeters had a pyruvic acid level above 2 mg. per hundred cubic centimeters, and 11 patients with a diphosphothiamine level below 3.5 micrograms had a pyruvic acid level averaging 2.7 mg. On the other hand, none of the patients with a diphosphothiamine level above 5 micrograms per hundred cubic centimeters had a pyruvic acid level above 1.8 mg. per hundred cubic centimeters. These results support the conclusions of Lu [42] and of Bueding, Wortis and Stern [43] that the pyruvic acid content of the blood is elevated in practically all cases of definite vitamin B_1 deficiency and is of aid in the diagnosis and the evaluation of the course of this deficiency.

Lactic Acid.—Only a few determinations of the lactic acid were performed, since the atmosphere around our hospital contained too many interfering substances for accurate results. The estimations were carried out at the Fatigue Laboratory (Harvard University) with the apparatus and method used by Edwards.[44]

The lactic acid content of the blood was elevated in 5 of 7 thyrotoxic patients in a resting and fasting state. Of 19 determinations on 3 subjects, it was elevated in all but 2 instances, occasionally being as high as 25 to 30 mg. per hundred cubic centimeters.

Magnesium.—Soffer and collaborators [45] found that in 35 of 50 patients with hyperthyroidism there was a definite increase in nondiffusible magnesium. Although the degree of this change was not consistently proportional to the height of the metabolic rate, there was a decrease in the nondiffusible magnesium with adequate iodine treatment, a further decrease with subtotal thyroidectomy and a drop to a subnormal level in myxedema. On the other hand, the administration of thyroid or thyroxin to myxedematous patients or thyroidectomized dogs resulted in a return of the magnesium to normal levels. Lavietes and Dine [46] confirmed these observations and found that in 7 patients with hypermetabolism without hyperthyroidism the protein-bound magnesium was uniformly normal. They suggested that magnesium may be an integral part of the circulating thyroid hormone or of the complex in which the hormone functions.

EFFECT ON CARBOHYDRATE METABOLISM OF TREATMENT WITH THIAMINE AND MAGNESIUM

The evidence thus far indicates that in the blood of most thyrotoxic subjects there is an accumulation of pyruvic acid, as well as of lactic acid, a decrease in the diphosphothiamine and an increase in the protein-bound magnesium. Since diphosphothiamine and magnesium are greatly concerned in the decarboxylation

43. Bueding, E.; Wortis, H., and Stern, M.: Pathological Variations in Blood and Spinal Fluid Pyruvic Acid, J. Clin. Investigation **21**:85, 1942. Bueding, E., and Wortis, H.: Pyruvic Acid in Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **44**:245, 1940.

44. Edwards, H. T.: A Simplified Estimation of Lactate in Normal Human Blood, J. Biol. Chem. **125**:571, 1938.

45. Soffer, L. J.; Dantes, D. A.; Grossman, E. B.; Sobotka, H., and Jacobs, M. D.: Ultrafiltrable Magnesium in Hyperthyroidism, J. Clin. Investigation **18**:597, 1939. Soffer, L. J.; Cohn, C.; Grossman, E. B.; Jacobs, M., and Sobotka, H.: Magnesium Partition Studies in Graves' Disease and in Clinical and Experimental Hypothyroidism, ibid. **20**:429, 1941.

46. Lavietes, P. H., and Dine, R. F.: The Relation of Magnesium to the Thyroid Hormone, J. Clin. Investigation **20**:444, 1941.

and oxidation of pyruvic acid, as stated, we performed a series of experiments on the effect on the carbohydrate metabolism of the administration of diphosphothiamine and magnesium to 7 patients with thyrotoxicosis, 2 with myxedema, 2 with neuritis associated with vitamin B_1 deficiency and 9 normal persons. The thyrotoxicosis was mild or moderate in 6 patients and severe in 1.

Changes in the levels of dextrose, pyruvate, lactate, thiamine and diphosphothiamine in the blood were observed at frequent intervals during a period of four hours following the injection of dextrose. The experiment was repeated several times, in order that we might observe these chemical changes after the injection of dextrose plus magnesium, dextrose plus magnesium plus diphosphothiamine, dextrose plus diphosphothiamine and diphosphothiamine without dextrose. The entire group of experiments was performed on some patients and only a few on others. Thus, not only were the responses in the different types of patients compared, but each patient served as a control for himself.

All the subjects had been receiving a high carbohydrate intake before the tests were carried out, and an interval of at least two to three days was permitted to elapse between tests. The patients were kept in a fasting and resting state while the experiments were performed. The specimens of blood were obtained from the arm which had not received the injections.

Effects of the Injection of Dextrose.—Fifty grams of dextrose in 50 per cent solution was injected intravenously over a period of six minutes. Specimens of blood were usually taken at the following times: during fasting and fifteen, forty-five, ninety, one hundred and fifty minutes and four hours after the administration of the dextrose.

For 3 of the thyrotoxic patients the dextrose tolerance curve was normal, but for the other 4 there were an elevated fasting level and a slower fall than normal; all of the dextrose levels determined forty-five, ninety and one hundred and fifty minutes after the injection of dextrose were above those of the normal persons at the corresponding times. The averages of these results have been plotted in chart 5. The dextrose tolerance curves of the myxedematous patients were almost identical with those of the thyrotoxic patients (chart 5) except that the specimens taken during fasting were normal. Of the 2 thiamine-deficient patients, 1 had a decreased dextrose tolerance, whereas the other had a normal response.

For a number of years it has been known that thyrotoxic subjects tend to show a decreased tolerance to dextrose.[47] It is not entirely clear as to why this is true, although a number of factors may be considered as possibly playing a role, e. g., starvation, vitamin B deficiency, hepatic damage and concomitant disease of the pituitary or pancreas.

John [48] found that diabetes was twice as common in patients with hyperthyroidism as in the general population, but in 38.7 per cent of the former the dextrose tolerance curve ultimately returned to normal, whereas it became normal in only 29.6 per cent of persons without hyperthyroidism. He noted that all of the thyrotoxic patients who had a normal dextrose tolerance curve before thyroidectomy continued to have a normal one indefinitely. The demonstration of the decreased dextrose tolerance in these patients long after thyroidectomy suggests that the pancreatic islets may have been exhausted, owing to the continued heavy demands placed on them, or that there is a persistence of hypertuitary activity.

47. Youmans, J. B., and Warfield, L. M.: Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency, Arch. Int. Med. **37**:1 (Jan.) 1926.

48. John, H. J.: Repeated Glucose Tolerance Tests in Hyperthyroidism, J. Clin. Endocrinol. **2**:264, 1942.

Bueding, Stein and Wortis [49] found a decreased dextrose tolerance in most patients with vitamin B_1 deficiency. We were unable to alter the dextrose tolerance curve of any of our patients by giving 5 mg. of diphosphothiamine intravenously just before performing the dextrose tolerance tests. It is of interest that 1 patient who repeatedly showed decreased dextrose tolerance had a normal response to dextrose after a thyroidectomy in spite of evidence of a moderate deficiency in vitamin B_1.

Weller [50] found a well marked chronic parenchymatous hepatitis in 22 of 44 selected patients with exophthalmic goiter, but only 1 example of the same degree of change was found in a control series of the same number of persons studied at autopsy. In fact, only 6 of the patients showed no hepatitis, whereas of the control series 30 of the total 44 showed no hepatitis. Furthermore, Youmans and Warfield [47] demonstrated an impairment of hepatic function in 50 per cent of the patients with thyrotoxicosis on whom they performed tests. They also found that 21 of 27 patients showed a decreased dextrose tolerance, but they stated that this, more than any other feature of the disease except loss of weight, was found to be related to the decreased efficiency in hepatic function.

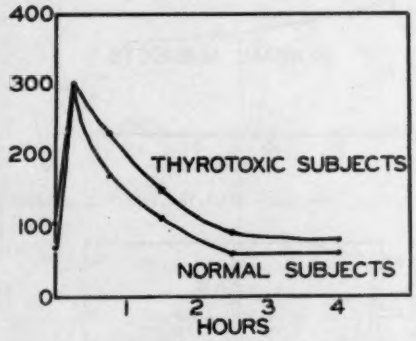

Chart 5.—Blood sugar curves (average) after the intravenous injection of 50 Gm. of dextrose in normal and in thyrotoxic subjects.

Vitamin B_1 deficiency, hepatic disease, depletion of the glycogen stores of the body and associated disease of the pituitary and pancreas probably account for many of the disturbances in the dextrose tolerance reactions that have been observed in thyrotoxic patients.

The changes in the level of pyruvic acid in the blood following infusion of dextrose were pronounced in all 7 thyrotoxic subjects. A marked rise occurred (chart 6) immediately after injection of the dextrose, and the level continued to rise for thirty to forty-five minutes, reaching a peak of 3 to 5 mg. per hundred cubic centimeters. The level was highest in 2 subjects at ninety minutes. In all but 1 subject it was still elevated at the end of one hundred and fifty minutes. However, in 7 normal persons tested it did not rise above 2.5 mg. per hundred cubic centimeters at any time and was essentially normal within ninety minutes. There was little rise in the pyruvate curve for the 2 myxedematous patients tested, the highest level being 1.9 mg. per hundred cubic centimeters. The response in

49. Bueding, E.; Stein, M. H., and Wortis, H.: Blood Pyruvate Curves Following Glucose Ingestion in Normal and Thiamine Deficient Subjects, J. Biol. Chem. **140**:697, 1941.

50. Weller, C. V.: Hepatic Lesions Associated with Exophthalmic Goiter, Tr. A. Am. Physicians **45**:71, 1930.

the patients with vitamin B_1 deficiency was similar to that in the thyrotoxic patients. Bueding, Stein and Wortis [49] have reported that in subjects with thiamine deficiency the level of pyruvate in the blood during fasting is elevated and that the pyruvate curve after ingestion of dextrose is abnormally elevated and is slow in returning to a normal level.

For a further test of the ability of thyrotoxic subjects to metabolize pyruvic acid, 5 Gm. of sodium pyruvate was prepared and injected intravenously according to the technic described by Wilkins, Weiss and Taylor.[51] Again it was demonstrated that these patients metabolize pyruvic acid distinctly more slowly than normal.

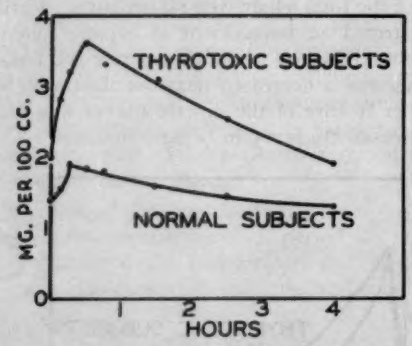

Chart 6.—Pyruvic acid curves (average) after the injection of dextrose in 8 normal and in 6 thyrotoxic subjects.

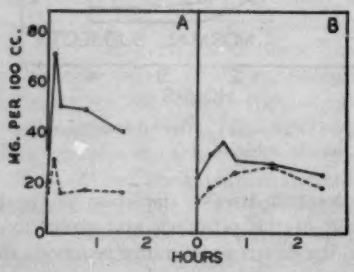

Chart 7.—Lactate curves (average) after the injection of sodium pyruvate (*A*) or dextrose (*B*) in 4 normal subjects (broken lines) and in 5 thyrotoxic patients (unbroken lines).

We found that in the thyrotoxic subjects, regardless of whether dextrose or sodium pyruvate was injected, the lactate of the blood rose to abnormally high levels and was slow in returning to normal (chart 7).

For four hours after the injection of dextrose the levels of diphosphothiamine and thiamine in the blood showed moderate fluctuation. However, the amount of these substances remained at definitely lower levels in the thyrotoxic subjects than in the normal persons (chart 8).

Effects of the Injection of Dextrose and Magnesium.—In order to study the effects of the decreased amounts of diffusible magnesium on the abnormal pyruvic

51. Wilkins, R. W.; Weiss, S., and Taylor, F. H. L.: The Effect and Rate of Removal of Pyruvic Acid Administered to Normal Persons and to Patients With and Without "Vitamin B Deficiency," Ann. Int. Med. **12**:938, 1939.

acid metabolism in thyrotoxic subjects, we saturated the patients with magnesium sulfate, repeated the dextrose injection and studied the resulting changes in the values for dextrose, pyruvate, lactate, free thiamine and diphosphothiamine in the blood.

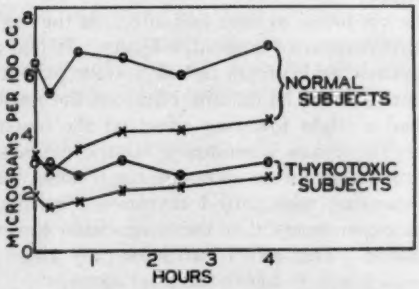

Chart 8.—Thiamine (X—X) and diphosphothiamine (O—O) curves (average) after the injection of dextrose in 5 normal subjects and 5 thyrotoxic patients.

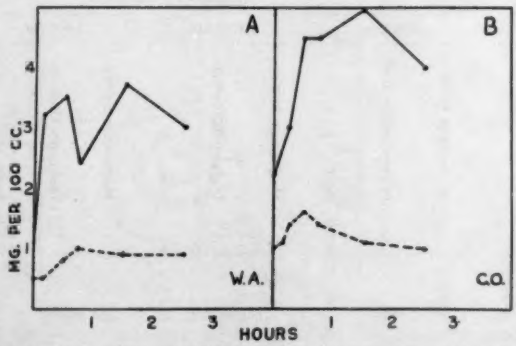

Chart 9.—The marked effect of diphosphothiamine in one case (A) and of magnesium sulfate in another (B) in preventing the rise of pyruvic acid after the intravenous injection of 50 Gm. of dextrose. The unbroken lines indicate dextrose and the broken lines dextrose plus diphosphothiamine (A) and dextrose plus magnesium sulfate (B).

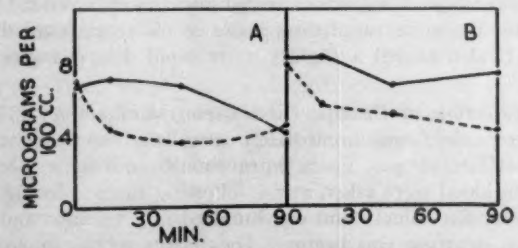

Chart 10.—The effect of magnesium sulfate in suppressing the diphosphothiamine curve after the injection of sodium pyruvate or dextrose. In A the unbroken line indicates sodium pyruvate and the broken line sodium pyruvate plus magnesium sulfate. In B the unbroken line indicates dextrose and the broken line dextrose plus magnesium sulfate.

One gram of magnesium sulfate in 50 per cent solution was given intramuscularly on the night preceding the test and again at 6 o'clock the next morning.

Either 0.5 or 1 Gm. was given intravenously immediately before the injection of dextrose. One gram was given about thirty minutes later and again about ninety minutes after the dextrose. The results were compared with those obtained when dextrose alone was injected.

The magnesium was not found to have any effect on the sugar tolerance curves of the thyrotoxic, myxedematous or normal subjects. It had a marked effect in preventing the rise in pyruvic acid content in 1 thyrotoxic patient (chart 9) and in 1 patient deficient in vitamin B but no definite effect on the normal or the myxedematous subjects. It had a slight lowering effect on the blood lactate content of 2 thyrotoxic subjects. There was a tendency for the magnesium to elevate the diphosphothiamine and thiamine curves, although the reverse was true in 2 patients, as shown in the accompanying table. In 1 thyrotoxic patient (chart 10), it was clear in three different experiments that the magnesium lowered the diphosphothiamine level in the blood. This effect lasted for only about forty-five minutes, but another injection was found to lower the level again.

Effect of Magnesium and Diphosphothiamine

		Changes * in the Blood										
		Dextrose			Pyruvate			Lactate				
Subjects		Magnesium Sulfate	Diphosphothiamine	Both	Magnesium Sulfate	Diphosphothiamine	Both	Magnesium Sulfate	Diphosphothiamine	Both	Diphosphothiamine Magnesium Sulfate	Thiamine Magnesium Sulfate
Thyrotoxic.....	W. A.	0	0	0	0	— — —	— —	—	..	—	— —	—
	C. O.	0	0	0	— — —	—	— —	—	— —	— —	+++	+++
	J. E.	0	..	0	+	..	±	..	..	..	+	+
Normal.....	C. D.	0	..	0	0	..	0	..	..	..	—	— —
	L. E.	0	..	..	0	..	..	..	..	..	+	+
	K. I.	0	..	0	0	..	0	..	..	..	+	+
	G. A.	..	0	..	..	—	..	..	..	..	..	..
Myxedematous....	W. E.	0	..	..	0	..	..	..	..	..	++	—
Vitamin B_1 neuritis	O. B.	0	..	—	— — —	..	— — —	..	..	..	++	±

* 0 indicates no effect; ±, a questionable effect; +, an elevating effect, and —, a depressing effect.

With 2 thyrotoxic patients the experiment was repeated, magnesium sulfate and 5 Gm. of sodium pyruvate being administered intravenously instead of dextrose. The magnesium caused a more rapid disappearance of lactate than did pyruvate alone (chart 11). It also caused a slightly more rapid disappearance of pyruvic acid.

Effects of the Injection of Dextrose and Diphosphothiamine.—The dextrose experiments were repeated, and immediately after the dextrose was injected 5 mg. of diphosphothiamine was given intravenously during a period of two minutes. Samples of blood were taken at the following times: during fasting and six, eight, fifteen, forty-five, ninety and one hundred fifty minutes and four hours after the injection of dextrose was begun. The results were compared with the ones obtained when dextrose alone was administered.

The diphosphothiamine had no effect on the blood sugar content in any subject. It exerted a marked depressing effect on the pyruvic acid of 1 thyrotoxic patient (chart 9) and a slight effect on another thyrotoxic and 1 normal person. It also tended to prevent the rise in the lactate of the blood of the 1 thyrotoxic subject tested.

Effects of the Injection of Dextrose, Magnesium and Diphosphothiamine.—The experiment was repeated, magnesium sulfate, dextrose and diphosphothiamine being given in the same manner as in the other experiments. However, these substances had no effect on the dextrose tolerance curve of any patient except the one with vitamin B_1 deficiency, in whom a lowering occurred. In this patient, as well as in 2 thyrotoxic ones, there was less accumulation of pyruvic acid in the blood than in the experiments in which dextrose alone was used. In 2 thyrotoxic subjects the magnesium and diphosphothiamine tended to prevent some of the rise in lactate content.

Effects of the Injection of Diphosphothiamine.—When 5 mg. of diphosphothiamine was given alone, intravenously, to 5 normal persons the pyruvic acid content of the blood rose from 0.3 to 0.8 mg. per hundred cubic centimeters above the fasting level within eight minutes but began to decline within fifteen minutes and was normal in forty-five minutes. However, of 3 thyrotoxic patients tested, in 1 the value for pyruvic acid simulated the normal; in 1 it rose from 1.3 mg. to 2 mg. per hundred cubic centimeters within fifteen minutes and remained there for two and one-half hours, while in the third it was 2.5 mg. per hundred cubic centimeters during fasting, dropped to 2.2 mg. in eight minutes and gradually rose

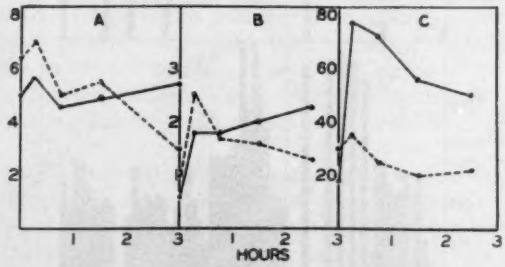

Chart 11.—The slight effect of magnesium on the diphosphothiamine (*A*) and pyruvate (*B*) curves and the marked effect on the lactate curve (*C*) after the administration of sodium pyruvate to 1 patient. The unbroken lines indicate sodium pyruvate and the broken lines sodium pyruvate plus magnesium sulfate. The diphosphothiamine is expressed in micrograms per hundred cubic centimeters and the pyruvate and lactate in milligrams per hundred cubic centimeters.

to the fasting level in the subsequent four hours. The diphosphothiamine had slight, if any, lowering effect on the blood sugar content of either the normal or the thyrotoxic subjects.

Summary.—Thus, magnesium and diphosphothiamine had definite effects on the levels of pyruvic acid, lactic acid, diphosphothiamine and thiamine in the blood. The effects varied in the different patients, although the same type of response was obtained repeatedly in the same person.

THIAMINE IN THE TREATMENT OF THYROTOXICOSIS

Means, Hertz and Lerman [6] have observed that the administration of vitamin B improves the clinical state of thyrotoxic subjects, although it does not have any definite effect on the basal metabolic rate. Frazier and Ravdin [33] have made similar observations. They found that when the vitamin B complex was used, there was a greater reduction in the pulse rate, a more rapid gain in weight and a shorter preoperative period.

During the last four years one of us (R. H. W.) has routinely prescribed brewers' yeast, 5 Gm. daily, and usually thiamine hydrochloride, 10 to 20 mg. daily, for all thyrotoxic subjects observed. The results confirm the ones described herein. Furthermore, the patients were found to experience a distinct subjective improvement.

Mild vitamin deficiencies commonly occur in thyrotoxicosis, and occasionally one sees severe ones. The latter tend to be resistant to treatment. For example, one of us (R. H. W.) has observed 4 thyrotoxic patients with coexisting pellagra, 2 with beriberi, one with neuritis and 2 with riboflavin deficiency, and to these patients it was necessary to give several times the dose of vitamins which one would have expected to give had they not had thyrotoxicosis.

To study this matter further we conducted thiamine balance studies with 5 thyrotoxic patients. In 4 of these patients the disease was mild, or moderate, and in the other it was severe. Each patient was kept in a metabolism ward but spent only part of the time in bed. The diets contained approximately 1 to 2 mg. of thiamine. Water was given as desired, and a record of the fluid intake and output

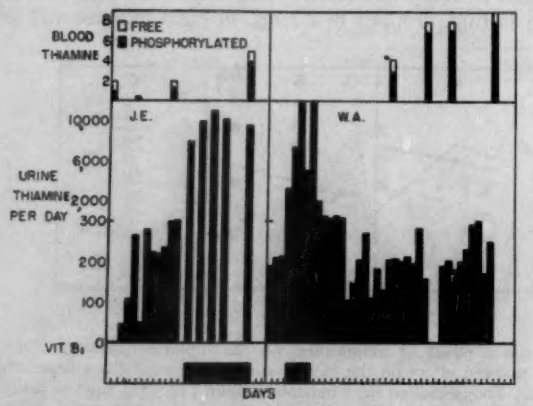

Chart 12.—Large amount of thiamine (milligrams) in the urine (cubic centimeters) in spite of the low thiamine and diphosphothiamine content (micrograms per hundred cubic centimeters) of the blood in 2 patients with thyrotoxicosis. The dose of vitamin B_1 was 10 mg. of thiamine hydrochloride twice daily given parenterally.

was kept. Total twenty-four hour specimens of urine were collected in 10 cc. of glacial acetic acid, and determinations of the thiamine content were performed according to the method of Egana and Meiklejohn.[52]

During the first two days, 4 subjects showed a daily excretion of thiamine in the urine of over 80 micrograms, but the other showed only traces. However, in spite of the fact that the urinary excretion of the vitamin was normal in 4 patients, the levels of diphosphothiamine and free thiamine in the blood were definitely low in each subject. These patients continued to excrete thiamine in the urine daily in quantities of about 200 micrograms in spite of a low level of thiamine in the blood (chart 12).

When 10 mg. of thiamine hydrochloride was given parenterally twice daily it was found that after about six to ten days the thiamine content of the blood became normal. However, 1 patient with hyperthyroidism was deficient after twelve

52. Egana, E., and Meiklejohn, A. P.: The Estimation of Thiamine in Urine, J. Biol. Chem. **141**:859, 1941.

days of such treatment (chart 12), and in 2 of the others the thiamine returned to a deficient level when the diet was not supplemented with vitamin B_1. This constant tendency for thyrotoxic patients to become deficient is due not only to the rapid destruction of this vitamin but to its loss in large quantities in the urine, sweat and stools.

Hardt and Still [53] have shown that when there is marked hyperhidrosis significant quantities of thiamine may be lost in the sweat. Since sweating is so common, and often marked, in thyrotoxic patients, it is probable that this accounts partially for the deficiency in thiamine in these persons.

Light, Schultz, Atkins and Cracas [54] have shown that when rats are in excretion equilibrium while receiving 15 or 515 micrograms of thiamine daily about 30 per cent is excreted in the urine and about 25 per cent in the feces. The total amount excreted in the feces increases in proportion to the intake.[55] Since in thyrotoxic subjects the motility of the gastrointestinal tract is abnormal and occasionally diarrhea is present, an increased fecal excretion of thiamine may be expected.

Just how much destruction of vitamin B_1 occurs in thyrotoxic subjects is not known, but it is probably a large quantity owing to the increased metabolism. Borsook and co-workers,[56] using thiamine containing radiosulfur, have shown that a considerable quantity of injected thiamine is destroyed and excreted in the urine as neutral sulfur compounds and inorganic sulfate. However, in addition to these degradation products there tend to be excess quantities of thiamine in the urine, as we have mentioned before. This is due, as Borson [35] has pointed out, somewhat to the marked diuresis shown by many thyrotoxic patients. In the patients whom we studied the daily excretion of urine averaged from 1,800 to 3,200 cc.

Ordinarily, as the body stores of thiamine become deficient, the quantity of this substance excreted in the urine becomes greatly reduced. For example, as shown in chart 13, 2 normal persons on a normal diet had an average daily excretion of 70 and 50 micrograms of thiamine, respectively. However, when their diet was reduced sufficiently to reduce the blood diphosphothiamine to a low level, 3 micrograms per hundred cubic centimeters, the urinary excretion of thiamine was less than 10 micrograms. On the other hand, a thyrotoxic subject with the same low level of diphosphothiamine in the blood, 3 micrograms, excreted an average of 185 micrograms daily for four days. It may be observed (chart 13) that the urinary volume was about twice as great in the thyrotoxic patient as in the normal subjects.

In addition to the foregoing factors which contribute to thiamine deficiency in thyrotoxic patients, one must consider the storage capacity of the tissues in these patients. Since this vitamin is stored in large part as diphosphothiamine, it is important to know, first, how well they can carry out phosphorylation of thiamine and, second, how well they can store the vitamin after phosphorylation.

We observed from our balance studies that sufficient phosphorylation occurred in the patients to permit a normal level of diphosphothiamine to develop in the blood within a period of about ten days. We also found that two minutes after

53. Hardt, L. L., and Still, E. N.: Thiamin in Sweat, Proc. Soc. Exper. Biol. & Med. **48**:704, 1941.

54. Light, R. F.; Schultz, A. S.; Atkins, L., and Cracas, L. G.: The Excretion of Vitamin B_1 in the Urine and Feces, J. Nutrition **16**:333, 1938.

55. Leong, P. C.: Vitamin B_1 in the Animal Organism: II. A Quantitative Study of the Metabolism of Vitamin B_1 in Rats, Biochem. J. **31**:373, 1937.

56. Borsook, H.; Buchman, E. R.; Hatcher, J. B.; Yost, D. M., and McMillan, E.: The Course of Thiamin Metabolism in Man as Indicated by the Use of Radioactive Sulfur, Proc. Nat. Acad. Sc. **26**:412, 1940.

the intravenous injection of 5 mg. of thiamine hydrochloride there was a marked rise in the diphosphothiamine content of the blood. No doubt many patients with thyrotoxicosis have more hepatic damage than did the ones we were working with, but we have demonstrated that in patients with severe Laennec's cirrhosis the phosphorylation of thiamine readily takes place. The liver is one of the main storehouses for thiamine. Therefore, since one often finds evidence of hepatic damage, the quantity of thiamine available in the body is probably reduced.

While the studies on thiamine balance were being performed on the patients previously mentioned as well as on 1 other patient, the basal metabolic rate and the weight of each patient were carefully followed, but these tended to remain the same.

Since 1 thyrotoxic patient noticed a feeling of well-being and marked relaxation after an injection of magnesium sulfate, it was decided to observe the effect of this substance on the basal metabolic rate. She was given 1 Gm. of magnesium

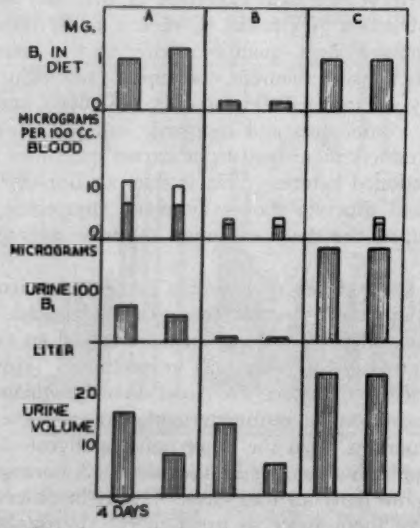

Chart 13.—*A* shows the values for 2 normal persons on a normal diet; *B*, the values for the same persons after they had been on a thiamine-deficient diet for several days (a diphosphothiamine content of the blood of only 3 micrograms per hundred cubic centimeters and a daily excretion of thiamine in the urine of about 15 micrograms); *C*, the values for a thyrotoxic patient, who had an equally low diphosphothiamine content of the blood but excreted about 185 micrograms daily. Each of the broad columns represents an average daily value for an interval of four days. The shaded blocks indicate diphosphothiamine and the clear portions thiamine.

sulfate intramuscularly three times daily for six days. No change in the metabolic rate was observed. Similar treatment of a myxedematous patient likewise was found to have no appreciable effect.

SUMMARY AND CONCLUSIONS

The interrelationship of cellular oxidations and the functions of the thyroid gland are discussed.

In the majority of a group of 40 unselected thyrotoxic subjects the levels of free thiamine and diphosphothiamine in the blood were below normal and that of pyruvic acid was elevated. In 5 of 7 of these patients the level of lactic acid was

elevated. The thiamine deficiency was regarded as being due to the waste of this substance in the stools, sweat and urine, as well as to the excessive combustion of food. Thyrotoxic patients tend to excrete relatively large amounts of thiamine in the urine in spite of a deficiency of this substance in the blood. The excessive excretion of thiamine in the urine is due partially to the diuresis which these patients experience. It is possible that thyrotoxic subjects cannot store as much thiamine as normal subjects because of the often coexisting hepatic and muscular disease. However, no impairment of the phosphorylation of thiamine was demonstrable.

During a period of four hours following the intravenous injection of 50 Gm. of dextrose or 5 Gm. of sodium pyruvate, the levels of pyruvic acid and lactic acid in the blood remained distinctly higher in thyrotoxic subjects than in normal persons. The response of the thiamine and diphosphothiamine in the blood varied, but these substances tended to remain at lower levels in thyrotoxic subjects than in normal ones.

Since patients with hyperthyroidism tend to have a decreased amount of diffusible magnesium and diphosphothiamine in the blood, the experiments with dextrose or sodium pyruvate were repeated immediately after 5 mg. of diphosphothiamine had been given or the patient had been saturated with magnesium sulfate. These substances had essentially no effect on the blood sugar content but in some instances had a marked effect on the blood pyruvate and lactate.

Administration of thiamine hydrochloride is of distinct advantage as an adjunctive measure in the treatment of thyrotoxicosis.

818 Harrison Avenue.

A MODIFIED TECHNIC FOR THE DETERMINATION OF SERUM BILIRUBIN

A PRELIMINARY REPORT OF ITS CLINICAL USE

B. SEPULVEDA, M.D.
Fellow in Medicine, Mayo Foundation
AND
ARNOLD E. OSTERBERG, PH.D.
ROCHESTER, MINN.

In a previous paper we[1] presented a modified technic for the determination of serum bilirubin. This technic possesses several technical advantages over the methods commonly in use and gives a more accurate evaluation of the concentration of the pigment. Furthermore, by this method the direct and indirect fractions can be measured separately. In this paper the results obtained from the clinical application of the new technic will be presented.

The method was used in a study of the behavior of the serum bilirubin of four different groups of persons: (1) normal persons and patients without evidence of hepatic disease; (2) patients who had hepatic disease but no jaundice; (3) patients in whose cases the result of the determination of the concentration of serum bilirubin and the result of the bromsulfalein test of hepatic function did not agree as to the presence of probable or proved hepatic disease and (4) patients who had parenchymatous, obstructive or hemolytic jaundice. The third group was included in order to study the correlation between the results of the bromsulfalein test and the values of indirect-reacting bilirubin in a small number of cases in which hepatic disease was suspected or proved to be present.

VALUES FOR BILIRUBIN IN THE SERUM OF NORMAL PERSONS AND PATIENTS WITHOUT DISEASE OF THE LIVER

The concentrations of bilirubin in the serum of 22 healthy technicians, nurses and physicians and in that of 63 patients who did not present clinical or laboratory evidence of hepatic disease were determined. Bilirubin giving the direct van den Bergh reaction was not found in the serum of any person in these two groups. The percentage incidence of each of the various concentrations of bilirubin giving the indirect van den Bergh reaction is shown in table 1. The concentrations varied from 0.1 to 0.8 mg. per hundred cubic centimeters of serum, but it should be emphasized that the values for bilirubin giving the indirect reaction were less than 0.6 mg. per hundred cubic centimeters in 95.5 per cent of cases.

VALUES FOR SERUM BILIRUBIN IN CASES OF HEPATIC DISEASE WITHOUT JAUNDICE

Values for serum bilirubin in 23 cases of disease of the liver without jaundice were determined (table 2). There were 12 cases of cirrhosis of the liver, 5 cases of myocardial failure and 6 cases of metastatic involvement of the liver. Bilirubin giving the direct van den Bergh reaction was not detected in any of these cases. In 10 of the 23 cases the concentration of bilirubin in the serum was more than

From the Division of Biochemistry, Mayo Clinic (Dr. A. E. Osterberg).
In this study Miss Elizabeth Maclay gave much technical assistance.
1. Sepulveda, B., and Osterberg, A. E.: Serum Bilirubin: A Procedure for the Determination of Indirect and Direct Values, J. Lab. & Clin. Med., to be published.

the upper limit (0.8 mg. per hundred cubic centimeters) of the range encountered in normal persons and patients who did not have hepatic disease. It was within the range (0.1 to 0.8 mg. per hundred cubic centimeters) found for persons without hepatic disease in the remaining 13 cases but the values in 11 of the 13 cases fell within the upper part of the range (0.6 to 0.8 mg. per hundred cubic centimeters) in which only 4.5 per cent of the values for persons without hepatic disease fell. In only 2 of the 23 cases were the values within the range (0.1 to 0.5 mg. per hundred cubic centimeters) of values in which 95.5 per cent of the values for persons without hepatic disease fell. Concentrations of bilirubin of more than 0.8 mg. per hundred cubic centimeters of serum are definitely abnormal; those of more than 0.5 mg. may be and probably are elevated above normal. Hepatic disease apparently may cause retention and increased concentration of bilirubin giving the indirect van den Bergh reaction without the appearance in the serum of bilirubin giving the direct reaction.

TABLE 1.—*Concentrations of Bilirubin Giving the Indirect van den Bergh Reaction in the Serums of Eighty-Five Persons Without Hepatic Damage* *

Bilirubin, Mg. per 100 Cc.	Percentage of 85 Cases
0.1	9.3
0.2	11.6
0.3	22.0
0.4	27.9
0.5	24.4
0.6	2.3
0.7	1.1
0.8	1.1

* In 45 cases of this series the bromsulphalein test was carried out and gave negative results.

TABLE 2.—*Concentrations of Bilirubin Giving the Indirect van den Bergh Reaction in the Serum in Twenty-Three Cases of Disease of the Liver in Which Bilirubin Giving the Direct Reaction Was Not Present*

Bilirubin, Mg. per 100 Cc.	Cases
0.0 to 0.2	1
0.3 to 0.4	1
0.5 to 0.6	..
0.7 to 0.8	11
0.9 to 1.0	4
1.1 to 1.2	3
1.3 to 1.4	1
1.5 to 1.6	2

In the normal state the balance between the production of bilirubin and its excretion by the liver is constant. The concentration of bilirubin in the serum of a normal person remains low and fluctuates in a narrow range. This balance between production and excretion of bilirubin is altered by a rise of the level of bilirubin giving the indirect van den Bergh reaction in two types of disorder. The first is hemolytic jaundice in which the overproduction of bilirubin giving the indirect reaction surpasses the excretory capacity of the liver. The second is hepatic damage. In this condition the formation of pigment is within normal limits but its excretion by hepatic cells is impaired. The increased quantity of serum bilirubin giving an indirect van den Bergh reaction in hemolytic conditions is well known, but little attention has been called to this increase in cases of hepatic injury.

Rozendaal, Comfort and Snell,[2] using the Thannhauser and Andersen technic for the determination of bilirubin in the serum, have reported the elevation of values for bilirubin giving the indirect reaction in cases of hepatic damage similar

2. Rozendaal, H. M.; Comfort, M. W., and Snell, A. M.: Slight and Latent Jaundice, J. A. M. A. **104**:374-379 (Feb. 2) 1935.

to those we studied. The new technic for the determination of values for bilirubin, which permits accurate measurement of small increases, provides definitely greater diagnostic possibilities from the study of bilirubin giving the indirect reaction than did the Thannhauser and Andersen technic. This study and our studies point to the possibility, and additional studies may prove, that an increase in the concentration of bilirubin giving an indirect reaction to more than 0.8 mg. and possibly to more than 0.5 mg. (modified technic) per hundred cubic centimeters of serum is an indication of injury to the liver when the relatively rare hemolytic and the familial type of jaundice have been excluded.

IS IT POSSIBLE THAT AN ELEVATION OF INDIRECT BILIRUBIN REVEALS HEPATIC DYSFUNCTION WHEN THE BROMSULPHALEIN TEST OF HEPATIC FUNCTION DOES NOT?

In order to obtain an answer to this question, determinations both of the concentration of bilirubin and of the retention of dye in the bromsulphalein test of hepatic function were made in a series of cases in which hepatic damage was suspected or proved. In none of these cases was bilirubin giving the direct van

TABLE 3.—*Values for Indirect-Reacting Bilirubin in Nine Cases in Which the Bromsulphalein Test of Hepatic Function Was Negative for Retention and Direct-Reacting Bilirubin Was Not Present*

Diagnosis	Bilirubin, Indirect Reaction, Mg. per 100 Cc.
Carcinoma of liver	0.9
Chronic alcoholism	0.8
Indeterminate splenomegaly	0.7
Residual infection of biliary tract	0.9
Chronic alcoholism	0.8
Chronic hepatitis	0.8
Gout	0.8
Myocardial failure	0.7
Chronic alcoholism	1.2

den Bergh reaction present. In about half of the cases in this group the bromsulphalein test did not disclose retention of dye; these are listed in table 3. In the other half of the group the bromsulphalein test revealed retention of dye and hepatic dysfunction, and these are listed in table 4.

In all the cases listed in table 3 the concentration of bilirubin was more than 0.6 mg. per hundred cubic centimeters of serum, that is, above the range of values (0.1 to 0.5 mg., inclusive, per hundred cubic centimeters) encountered in 95.5 per cent of persons who did not have hepatic disease. In 3 of the 9 cases listed in table 3 the values were above the upper limit (0.8 mg.) of the values of persons without hepatic disease. In short, while the values for bilirubin were not greatly elevated, they were definitely within the range indicating retention of bilirubin and possible hepatic damage, as was suggested by clinical appraisal in most of these cases. The bromsulphalein test, however, failed to disclose hepatic damage. In the cases listed in table 4 the values for bilirubin were within the range (0.1 to 0.5 mg., inclusive, per hundred cubic centimeters of serum) of 95.5 per cent of persons without hepatic disease and did not suggest hepatic damage, while the bromsulphalein test disclosed retention of dye as was expected from clinical appraisal in most of the cases.

It is clear that the two functions of the liver, the excretion of bilirubin and that of dye, do not behave in a parallel fashion and that bilirubin may be retained in the serum by damage to the liver when dye is not and vice versa. While

Snell and Magath [3] have shown that the bromsulphalein test is one of the most reliable tests of hepatic function in the absence of jaundice, it has been recognized that the test fails at times to reveal damage to the liver. The determination of the concentration of indirect-reacting bilirubin may prove to be a valuable accessory to the bromsulphalein test in the detection of damage of the liver in cases in which jaundice is not encountered and the direct-reacting bilirubin is not present.

VALUES OF BILIRUBIN IN CASES OF VARIOUS TYPES OF JAUNDICE

Values for bilirubin giving both the direct and the indirect van den Bergh reaction were determined in 25 cases of intrahepatic jaundice, 40 cases of obstructive jaundice, 8 cases of congenital hemolytic icterus, 1 case of so-called familial jaundice and 1 case of pernicious anemia with jaundice. Bilirubin giving the

TABLE 4.—*Values for Indirect Reacting Bilirubin in Ten Cases in Which the Bromsulphalein Test of Hepatic Function Showed Function to Be Abnormal and Direct-Reacting Bilirubin Was Not Present*

Diagnosis	Bilirubin, Indirect Reaction, Mg. per 100 Cc.	Bromsulphalein Test, Grade *
Chronic alcoholism	0.4	2
Chronic alcoholism	0.5	1
Gout	0.4	1
Inoperable gastric carcinoma	0.5	1
Hyperthyroidism	0.5	1
Chronic alcoholism	0.3	2
Abdominal carcinomatosis involving liver	0.2	2
Chronic alcoholism	0.3	1
Gastric carcinoma, liver metastasis (?)	0.3	3
Gout	0.3	2

* Grading is on a basis of 1 to 4 in which 1 indicates minimal and 4 maximal retention of dye.

TABLE 5.—*Comparison of Values for Serum Bilirubin in Cases of Intrahepatic and Cases of Obstructive Jaundice*

		Bilirubin, Mg. per 100 Cc.			
		Direct Reaction		Indirect Reaction	
	Cases	Range	Average	Range	Average
Intrahepatic jaundice	25	1.9-70.0	14.7	0.4- 5.0	1.8
Obstructive jaundice	40	1.2-93.0	18.6	0.1-10.0	1.9

indirect reaction only was found in the cases of hemolytic jaundice by the new modified technic, while in 5 of these cases the van den Bergh reaction was reported direct when the Thannhauser-Andersen technic was used. The not infrequent confusion in diagnosis arising from such falsely direct van den Bergh reactions is eliminated by the modified technic used in this study.

Bilirubin giving both the indirect and the direct van den Bergh reaction was measurable in every case of intrahepatic and every case of obstructive jaundice. The ranges of values and the average values for both tests of bilirubin in the cases of intrahepatic and the cases of obstructive jaundice are given in table 5. Several investigators, including Varela Fuentes and Viana,[4] Bengolea, Velasco Suárez and Raíces [5] and Franke,[6] among others, have stated that the separate

3. Snell, A. M., and Magath, T. B.: The Use and Interpretation of Tests for Liver Function, J. A. M. A. **110**:167-174 (Jan. 15) 1938.

4. Varela Fuentes, B., and Viana, C.: Les bilirubines, directe et indirecte du sérum dans les ictères aigus fébriles et dans les ictères chroniques, Compt. rend. Soc. de biol. **116**:1187-1192, 1934.

(Footnotes continued on next page)

determination of bilirubin giving the direct and of bilirubin giving the indirect reaction is useful in the differential diagnosis of obstructive and of intrahepatic jaundice. These authors assumed that the damage to the hepatic parenchyma impaired the excretion of bilirubin and raised the concentration of this fraction in the serum more than obstructive jaundice. We have been unable to confirm their results with our new technic. In our cases, obstruction of the common bile duct raised the average concentration of bilirubin giving the indirect reaction to 1.9 mg. per hundred cubic centimeters, while parenchymatous damage to the liver raised the average concentration to 1.8 mg. These average concentrations are so similar that a differential diagnosis between the two types of jaundice could not be made on this basis in our cases. Heilbrun and Hubbard [7] have reported results similar to ours. In our studies, moreover, the highest concentration of bilirubin giving the indirect reaction was found in a case of obstructive jaundice, not in a case of intrahepatic jaundice. The similarity of behavior of bilirubin giving the indirect reaction in the two types of jaundice may be due to the frequent appearance of parenchymatous damage secondary to the obstruction. The diagnostic importance of the concentration of indirect-reacting bilirubin deserves more study in a larger number of cases.

SUMMARY AND CONCLUSIONS

A preliminary report of the clinical use of a new technic for the determination of bilirubin in the serum has been made.

The concentrations of bilirubin in the serum of normal persons and of patients who did not have hepatic disease ranged from 0.1 to 0.8 mg. per hundred cubic centimeters of serum. The concentrations were 0.5 mg. or less in 95.5 per cent of these persons. The van den Bergh reaction of the serum of all these persons was indirect.

Values for bilirubin giving the indirect van den Bergh reaction may be slightly elevated in cases of hepatic disease without jaundice in which serum bilirubin giving the direct van den Bergh reaction is not found, and this rise apparently may indicate hepatic damage when hemolytic jaundice is excluded. The values may be elevated when the bromsulphalein test of hepatic function does not disclose dysfunction of the liver, and the new technic apparently may indicate hepatic dysfunction when the bromsulphalein test does not.

The concentration of bilirubin giving the indirect van den Bergh reaction is increased in obstructive and in intrahepatic jaundice as well as in hemolytic jaundice. The average concentration of bilirubin giving the indirect van den Bergh reaction in our cases of obstructive jaundice was similar to that in our cases of intrahepatic jaundice. The highest concentration of bilirubin giving the indirect van den Bergh reaction in our series was 10 mg. per hundred cubic centimeters of serum and was found in a case of obstructive jaundice, whereas the highest concentration in a case of intrahepatic jaundice was 5 mg. From our study it appears that the difference in the height of the concentration of bilirubin giving the indirect van den Bergh reaction in obstructive and in intrahepatic jaundice is not sufficiently distinctive to aid in the differential diagnosis of these two types of jaundice.

5. Bengolea, A. J.; Velasco Suárez, C., and Raíces, A. E.: El dosaje de la bilirrubina directa e indirecta en el suero sanguíneo. Su importancia en cirugia hepato-biliar, Prensa méd. argent. **23**:85-102 (Jan. 8) 1935.

6. Franke, K.: Klinische und lebendmikroskopische Untersuchungen der gestörten Leberfunktion: II. Gallenfarbstoffuntersuchungen bei Lebererkrankungen mit Ikterus, Ztschr. f. klin. Med. **130**:193-221 (March) 1936.

7. Heilbrun, N., and Hubbard, R. S.: Measurement of Chloroform-Soluble Fraction of Bilirubin in Persons with Jaundice and Its Significance, J. Lab. & Clin. Med. **26**:576-581 (Dec.) 1940.

MILESTONES IN THE DIAGNOSIS AND TREATMENT OF GOUT

E. NEUWIRTH, M.D.
NEW YORK

Gout is one of the oldest diseases recorded. A description of it is found as early as the fifth century B. C. in the writings of Hippocrates.[1] Despite its antiquity, there is much that is still unknown. The term gout is derived from the Latin *gutta,* a drop. According to Antonius Guainerius,[2] of the faculty of Pavia (fifteenth century), *gutta* signifies a humor that trickles downward from the head on some internal organ. It also indicates an articular pain, because the humor enters the joints in a manner resembling raindrops dripping from trees and housetops. The Greeks called gout ποδάγρα (a trap), because it grips the patient's foot as a trap grips the foot of an animal.[3]

The first use of the term *gutta* to designate gout is erroneously credited to Ralph Bocking (Radulphus),[4] who about 1270 wrote a biography of St. Richard of Wyche, bishop of Chichester, England. Bocking, who was the confessor of the bishop, mentioned a servant in the latter's household who was cured of his gout (*gutta quam podagram vel arteticam vocant*) by donning the bishop's boots. However, the word gout appears in earlier writings. Geoffroi de Villehardouin,[5] the famous French historian, used it in his "Histoire de l'empire de Constantinople sous les empéreurs françois," written between 1207 and 1212. The author related that the count Hugues de Saint Paul had "a grand malady of gout" (*une grant maladie de gote*) in his feet and knees and that he died of it. Physicians in medieval times were reluctant to use the term.[6] Nevertheless, it does appear in the learned works of prominent members of the Medical School of Salerno in the twelfth century. In a prescription from the *antidotarium* of Nicolaus Salernitanus[7] it is stated that *benedicta,* which contains hermodactyl as an ingredient, is of value for arthritic gout and podagra. Archimataeus, another member of the Salerno school in the twelfth century, wrote:

Gutta in diversis locis nascitur, sed maxime in iuncturis et cubitis, anchis, genibus, et articulis manuum, genuum et pedum, et dicitur gutta quia de humoribus paulatim et guttatim ad partes illas reumatizantibus habet fieri.[8] (Gout [gutta] occurs in various parts of the body but chiefly in the joints, in the elbows, in the hips, in the knees and in the joints of the hands and

1. Hippocrates: The Genuine Works of Hippocrates, translated from the Greek by Francis Adams, New York, W. Wood & Co., 1886.

2. Guainerius, Antonius: De juncturis sive de arthretica et calculosa passione commentariolus, in Opera Medica, Pavia, Antonius de Carchano, 1481.

3. Lucianus: Podagra tragice, in Sennert,[23] pp. 967-970.

4. Bocking, R., in Acta sanctorum Aprilis, Collecta, digesta, illustrata a Godefrido Henschenio et Daniele Papebrochio e Societate Iesu, Antwerp, apud Michaelem Cnobarum, 1675, book 1.

5. Villehardouin, G.: Histoire de l'empire de Constantinople sous les empéreurs françois, edited by Charles du Fresne du Cange, Paris, Imprimerie Royale, 1657.

6. Delpeuch, A.: La goutte et le rhumatisme, Paris, G. Carré & C. Naud, 1900.

7. Nicolaus Salernitanus: Antidotarium, Pavia, Franciscus de Sancto Petro, 1478-1479.

8. Archimataeus: De instructione medici secundum Archimathaeum, in Collectio salernitana, Naples, publicati a curo di Salvatore de Renzi, 1859, vol. 5, pp. 333-349.

the feet. The disease is called gout because it is caused by rheumy humors that flow slowly and drop by drop to the parts mentioned.)

For treatment, the author recommended pills containing hermodactyl, i. e., Colchicum autumnale, or meadow saffron.[9]

Thomas Sydenham[10] (1624-1689), whom Trousseau styled "the English Hippocrates,"[11] represents the first milestone that looms high on the crossroads between the old knowledge of gout and the new. It was he who recognized gout as a clinical entity and clearly distinguished it from other forms of arthritis and from rheumatism. This was, indeed, a remarkable advance that becomes all the more impressive when one realizes that even the celebrated Boerhaave,[12] who died fifty years after Sydenham, failed to make any clear and definite distinction between gout and arthritis.

Sydenham gave a colorful and dynamic description of the attack of acute gouty arthritis. He said that the fit thunders on the patient usually without warning about 2 o'clock in the morning, seizing the great toe, the heel or the ankle. The pain is like that caused by a dislocated bone or the gnawing of a dog and is not relieved by position or warmth. The affected part is unable to bear the weight of the clothes on it or the "hard walking in the chamber." The part is swollen and hot; the veins are engorged. The complete symptomatic recovery that follows the acute arthritic episode is expressed in these words: "Within a few days the other Foot will be in pain as the former was; and if the former has left off aking, the Weakness which rendred it infirm will presently vanish, Strength and perfect Health being so presently restored, as if it never had been out of order."

Such an acute attack of articular gout may last from a few days to a week or more. After an asymptomatic interval of weeks, months or, generally, one or more years, the attacks recur involving the same or other joints. Such recurrent attacks of acute arthritis appearing suddenly, developing swiftly and disappearing rapidly and completely afford a most valuable clue in the diagnosis of "pretophaceous" or presumptive gout. One of the reasons that gout remains unrecognized in so many cases is the insistence on the presence of podagra, i. e., acute involvement of the metatarsophalangeal joint of the great toe. Although this occurs in the majority of the cases in the original attack of the disease, any joint of the foot or other part of the body may be affected at the onset. Even in late seizures, which are usually polyarticular, podagra may be absent.

Early attacks of gout are usually monarticular, but exceptions are not uncommon; the disease may involve several joints even at the onset. Acute attacks of gout with involvement of multiple joints, especially when they occur in younger persons and are acompanied by fever, leukocytosis and an increased sedimentation rate, are often mistaken for rheumatic fever. The absence of heart disease, tachycardia and nosebleeds favors the diagnosis of gout. Another differential point is the peeling of the skin over affected joints following subsidence of inflammation.

9. The use of the word *gutta* goes far beyond the twelfth century. Thietmar, Bishop of Merseburg (976-1018), employed it: "Fuit olim Godescalki abbatis quidam monachus nomine Aloricus cui in capite suo multum nocuit migraena, aut ex gutta, aut ex vermibus" (Thietmari merseburgensis episcopi chronicon, in Monumenta Germaniae historica, Scriptores rerum Germanicarum, Berlin, 1935, new series, book 9).

10. Sydenham, T.: The Whole Works of That Excellent Practical Physician, Dr. Thomas Sydenham, translated from the Latin by John Pechy, London, R. Wellington & E. Castle, 1696.

11. Trousseau, cited by Llewellyn.[87c]

12. Boerhaave, H.: Aphorisms Concerning the Knowledge and Cure of Diseases, translated from the Latin edition by J. Delacoste, London, Innys & Hitch, 1742.

This is seen in gout and not in rheumatic fever. Postoperative flare-ups of rheumatic fever appear later [13]; those of gout, earlier.[14]

Other conditions from which acute gouty arthritis has to be differentiated are the following: gonorrheal, acute traumatic, rheumatoid and suppurative arthritis, intermittent hydrarthrosis, acute bursitis and septic cellulitis. The clinical course characteristic of early gouty arthritis, i. e. recurrent attacks and complete symptomatic recoveries, and the prompt favorable response to the early administration of full doses of colchicum should offer no difficulty in establishing the diagnosis of gout. A high concentration of urates in the blood and a family history of gout are additional corroborative diagnostic aids.

Not infrequently acute attacks of gout are provoked by major or minor trauma, operative procedure, overuse of joints, exposure to cold and damp, inordinate drinking, overeating, hunting or fishing expeditions, hiking, treatment at a spa, excessive sexual indulgence, mental strain, emotional stress, ingestion of drugs (mersalyl,[15] ergotamine tartrate,[14] liver extract,[16] gold,[17] dehydrocholic acid [18] and thiamine hydrochloride [19]), purging, severe hemorrhage or transfusion. This should be borne in mind in obtaining the history of a person with acute arthritis. Other conditions often preceding acute gouty attacks are renal colic and olecranal bursitis. The diagnosis of gout should be entertained if, in addition, the history reveals that the attack occurred during the early spring or fall, appeared suddenly in the early morning hours and involved a distant joint (feet, ankles, hands or wrists), especially the great toe. The spine, shoulders and hips are rarely affected. Bald, obese men of ruddy complexion [20] and in the fourth or fifth decade of life are particularly prone to have this disease (gout is uncommon in women and in young persons). A combination of the features described is almost pathognomonic of gout.[14]

The diagnosis of advanced gout is not difficult. After repeated acute seizures for many years, intra-articular structural changes develop and chronic arthritis, with permanent distortion of the joints and occasionally ankylosis, ensues. At this stage there is usually an elevated concentration of urates in the blood, tophaceous deposits of sodium urate crystals are present and frequently punched-out areas of osseous erosion may be revealed in the roentgenograms of the feet and hands. This stage is not reached, however, before ten or twelve years. If one were to wait for the development of these classic changes before making a diagnosis of gout, much valuable time would be lost during which the institution of

13. Ludwig, A. O.; Bennett, G. A., and Bauer, W.: A Rare Manifestation of Gout: Widespread Ankylosis Simulating Rheumatoid Arthritis, Ann. Int. Med. **11**:1248-1276 (Jan.) 1938.

14. Hench, P. S.: A Clinic of Some Diseases of Joints, M. Clin. North America **19**: 551-583 (Sept.) 1935; Comments on the Diagnosis and Management of Gout in Certain Parts of the United States, Proc. Staff Meet., Mayo Clin. **12**:262-269 (April 28) 1937; Diagnosis and Treatment of Gout and Gouty Arthritis, J. A. M. A. **116**:453-459 (Feb. 8) 1941.

15. Price, N. L.: Gout Following Salyrgan Diuresis, Lancet **1**:22-23 (Jan. 7) 1939.

16. (*a*) Deitrick, J. E.: The Association of Congenital Hemolytic Icterus and Gout, Internat. Clin. **3**:264-277 (Sept.) 1940. (*b*) Opsahl, R.: Hematopoiesis and Endogenous Uric Acid, Acta med. Scandinav. **102**:611-628, 1939.

17. Pringle, G. L. K.: Discussion on the Skin Manifestations in Rheumatism and Gout, Proc. Roy. Soc. Med. **31**:712-715 (April) 1938.

18. Bowers, J. M.: Gout, Northwest Med. **27**:284-288 (Sept.) 1938.

19. Vorhaus, M. G., and Kramer, M. L.: Studies on Thiamin Chloride, Tr. Am. Therap. Soc. **38**:109-115, 1938.

20. Kinell, J., and Haden, R. L.: Gout: A Review of Sixty-Two Cases, M. Clin. North America **24**:429-441 (March) 1940.

appropriate therapy might result in the postponement of serious renal, cardiovascular and cerebrovascular complications. Gout is more common in the United States than is generaly supposed,[21] but unfortunately the disease remains unrecognized for many years. In 40 cases reported from the Mayo Clinic, the average duration was fifteen years.[14]

Sydenham [10] stated the belief that gout was caused by some "morbifick" matter and that the attacks represented nature's way of disposing of the evil substance by removing it into the joints. For this reason he did not approve of attempts to check the acute attack and to curb the natural development of the disease. Boerhaave [12] wrote:

> Nothing can be more prejudicial in this Disease than to hinder the matter of the Gout . . . from flowing freely to its proper Places. . . . For if the same be retained and hindered, it creates Apoplexies, Palsies . . . and many more wonderful and often suddenly mortal Diseases. They'll not give way unless you bring on a new and smart Fit of the Gout. . . .

Meade [22] expressed this idea in an epigram: "Gout is the only cure of gout." This view goes back to Hippocrates, who taught that organisms are their own physicians. No wonder Emperor Charles V said: "Patience and some crying are the best drugs for gout." [23]

Garrison [24] wrote that Sydenham "stood apart from all medical theorizing and scientific experimentation of his time; disregarded all his predecessors except Hippocrates. He knew nothing of Vesalius, Harvey and Malpighi. His four favorite books were Hippocrates, Cicero, Bacon, and Don Quixote." It seems, however, that another book should be added to Sydenham's library, a book no one ever mentions, much less praises.[6] This excellent volume is called "Tractatus de arthritide;[23] it was published in 1631, at which time Sydenham was 7 years old. The author was Daniel Sennert (1572-1637), called by his contemporaries a second Galen. Sennert stated the belief that the cause of gout is a morbid humor within the blood vessels resembling the nature of spirits or salts and produced by the liver, spleen and stomach. "Call it bile, pituite, bile mixture, salt, tartar, or whatever pleases you, I consent, provided the thing is well explained," wrote Sennert.

It was not until two hundred years later that more was learned about the "morbifick" matter mentioned by Sydenham, the substance for which Sennert had no name. In 1848, Alfred Baring Garrod [25] reported that the blood of gouty persons contains abnormal quantities of uric acid in the form of sodium urate and that this is due to the inability of the kidneys to excrete uric acid. He expressed the view that gout results from renal insufficiency. Although knowledge regarding the role of the kidneys in gout is still inadequate, it is believed that defective renal function is the result rather than the cause of gout.

Garrod's discovery marks another milestone of overwhelming importance on the road to the newer knowledge of gout. It stimulated extensive research into

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21. (*a*) Cohen, A.: Gout, Am. J. M. Sc. **192**:488-493 (Oct.) 1936; Gout Among Arthritics, Pennsylvania M. J. **41**:1100-1104 (Sept.) 1938. (*b*) Hench.[14] Kinell and Haden.[20] Vorhaus and Kramer.[19]

22. Meade, cited by Llewellyn.[37e]

23. Sennert, D.: Opera, Lugduni, Io. Antonius Huguetau and Marius Antonius Ravaud, 1666, book 4.

24. Garrison, F. H.: An Introduction to the History of Medicine, ed. 4, Philadelphia, W. B. Saunders Company, 1929.

25. Garrod, A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, Med.-Chir. Tr., London **31**:83-97, 1848; The Nature and Treatment of Gout and Rheumatic Gout, London, Watson & Maberly, 1859.

the biochemistry of the disease. However, it is a pity that therewith the problem of gout was transferred from the ward to the laboratory, where it still remains. In 1776, Scheele,[26] a Swedish chemist, demonstrated uric acid in urinary calculi. Twenty-one years later, William Hyde Wollaston[27] analyzed the material obtained from tophi and found that it contained lithic or uric acid. Prior to this, tophi were believed to be made up of chalk and were called chalk stones. This trend of research was brought about by the belief that there is a close relationship between gout and urinary calculi because both conditions often occur simultaneously in the same person. Sydenham,[10] who himself suffered from both diseases, aptly remarks that "gout breeds the stones in very many."

To demonstrate urate in the blood, Garrod[25] devised a simple method known as the "thread experiment." Sodium urate, when present in excess in the blood, will crystallize and adhere to a thread placed in the serum. If the amount of urate is normal, crystals will not form. Some authorities[28] still prefer the crystallographic method of demonstrating blood urates to chemical methods. The normal value for urates determined by the Folin (1930) method varies from 2 to 4.5 mg. per hundred cubic centimeters of whole blood. It has been suggested that estimations of urates be carried out on serum derived from blood allowed to clot under oil.[29] With this technic, Jacobson[29] found a serum urate level exceeding 6 mg. per hundred cubic centimeters in almost all his gouty patients. The implication appears to be that high values for serum urates are practically always present in established gout.[30] In the experience of others, however, the concentration of blood urates may be normal even in patients with tophaceous gout.[31] Hyperuricemia is infrequent, especially in the early years of the malady. On the other hand, an elevated level of blood urates cannot be considered pathognomonic of gout, because it occurs in a variety of other diseases, such as pneumonia, leukemia, polycythemia, renal insufficiency and acute infections.

The cause of hyperuricemia in gouty subjects is unknown. Increased formation,[32] diminished destruction and deficient excretion of urates have been incriminated. As yet no convincing evidence has been furnished to lend solid support to any of these hypotheses. Destruction of nuclear material, the mother substance of uric acid, is not increased in gout, nor does uricolysis occur in human subjects.[33] Since the observations of Garrod, it has been claimed again and again that the excretion of urates is retarded by some renal condition causing their retention and accumulation in blood, tissues and joints. Points against the renal origin of gout are: 1. Patients with glomerulonephritis and associated hyperuricemia do

26. Scheele, K. W.: Chemical Essays, translated by T. Beddoes, from the Transactions of the Academy of Sciences at Stockholm, London, J. Murray, 1786, essay IX.

27. Wollaston, W. H.: On Gouty and Urinary Concretions, Phil. Tr. **2**:386-400, 1797.

28. Weil, M. P.: Considérations sur la goutte aiguë, sa fréquence, les tests de Garrod, ses formes cliniques, son évolution radiologique, Ann. méd.-chir. **4**:45-53, 1939.

29. Jacobson, B. M.: The Uric Acid in the Serum of the Gouty and of Non-Gouty Individuals: Its Determination by Folin's Recent Method and Its Significance in the Diagnosis of Gout, Ann. Int. Med. **11**:1277-1295 (Jan.) 1938.

30. Jacobson.[29] Ludwig, Bennett and Bauer.[18]

31. (*a*) Gibson, H. J., and Kersley, G. D.: Gout, M. Press **196**:353-361 (April 27) 1938. (*b*) Kinell and Haden.[20]

32. Talbott, J. H., and Coombs, F. S.: Metabolic Studies on Patients with Gout, J. A. M. A. **110**:1977-1982 (June 11) 1938. Talbott, J. H.; Jacobson, B. M., and Oberg, S. A.: The Electrolyte Balance in Acute Gout, J. Clin. Investigation **14**:411-421 (July) 1935.

33. Thannhauser, S. J.: Lehrbuch des Stoffwechsels und der Stoffwechselkrankheiten, Munich, J. F. Bergmann, 1929. Thannhauser, S. J., and Hemke, W.: Besteht bei Gicht eine funktionelle Störung der Harnsäureausscheidung? Klin. Wchnschr. **2**:65-67 (Jan. 8) 1923.

not have gout. 2. Large numbers of gouty patients do not present evidence of anatomic renal lesions. 3. Urates are abundantly excreted at the height of and immediately after acute attacks of gout. The possibility of a functional renal disturbance causing an insufficient elimination of urates only has been offered as a reason for the high concentration of urates in the blood and the evolution of gout.[33] It has been suggested recently that a functional disturbance of the vegetative nervous system involving renal innervation may have etiologic significance in the disease.[34] Another theory is that congenital or acquired difficulty in the elimination of purines because of loss of the power to conjugate them suitably may be the cause of hyperuricemia in gouty patients.[35] Recent studies fail to disclose difference in urate clearance in gouty and in nongouty persons.[36]

Widespread opinion holds gout to be an expression of disturbed purine metabolism. But in gouty patients there is no break or flaw in the chain of intermediary purine metabolism.[23] The aminopurines, adenine and guanine, are deaminated to hypoxanthine and xanthine, which, in turn, are oxidized to uric acid. Hence, uric acid is regarded as a by-product of normal metabolic processes.

According to Garrod,[25] acute attacks of gouty arthritis are caused by precipitation of sodium urate crystals in and around joints. However, it does not seem that uric acid is involved in provoking acute attacks. At least, the hyperuricemia caused by retention, in acute or chronic nephritis, or by excessive formation of uric acid, as in leukemia, does not invoke attacks of acute arthritis. Furthermore, injection of urates into veins or body tissues is painless; such injection does not provoke acute articular exacerbations in a gouty person, nor does it aggravate existing gouty arthritis. Finally, the pain in acute gouty arthritis is alleviated by colchicum, which has no action on the urates in the blood or urine.

Sennert [23] mentioned in his treatise written three hundred years ago that Julius Alexandrinus knew a gouty person who suffered an acute attack each time he consumed carp. Today some physicians [37] envisage gout as an allergic reaction to an exogenous or endogenous allergen. The allergen may be derived from food, drink or bacteria or may represent tissue substance which forms after trauma or an operation. The purine content of foods and drinks does not seem to play a role. As yet there is insufficient evidence to warrant the assumption that food or other allergens are the cause of gout.

Tophi are the sole pathologic proof of gout. They establish the gouty nature of an associated arthritis. Galen [38] (131-200 A. D.) seems to have been the first to describe them. In his opinion, tophi result from a crude humor becoming inspissated and viscous. Actually, tophi represent deposits of sodium urate crystals

34. Grabfield, G. P.: A Pharmacologic Study of the Mechanism of Gout, Ann. Int. Med. **11**:651-656 (Oct.) 1937. Grabfield, G. P., and Pratt, J. H.: Action of Cincophen, J. Pharmacol. & Exper. Therap. **42**:407-439 (Aug.) 1931.

35. Langdon-Brown, W.: Gout, M. Press **196**:331-334 (April 20) 1938.

36. (*a*) Brøchner-Mortensen, K.: Uric Acid in Blood and Urine, Acta med. Scandinav. (supp.) **84**:1-269, 1937; On Variations in Uric Acid Clearance After Administration of Purine, with Special Reference to the Threshold Problem, ibid. **99**:525-537, 1939. (*b*) Coombs, F. S.; Pecora, L. J.; Thorogood, E.; Consolazio, W. V., and Talbott, J. H.: Renal Function in Patients with Gout, J. Clin. Investigation **19**:525-535 (May) 1940.

37. (*a*) Lichtwitz, L.: Gout, Bull. New York Acad. Med. **10**:306-319 (May) 1934. (*b*) Llewellyn, L. J.: The Etiology of Gout, New York M. J. **118**:601-608 (Nov. 21) 1923. (*c*) Llewellyn, L. J., and Beaumont, W. M.: Gout, St. Louis, C. V. Mosby Company, 1921. (*d*) Gudzent, F.: Gicht und Rheumatismus, Berlin, Julius Springer, 1928. (*e*) Widal, F.; Abrami, P., and Joltrain, E.: Les cuti-réactions aux vins chez les goutteux, Presse méd. **33**:1425-1426 (Oct. 28) 1925.

38. Galen, C.: Opera omnia, editionem curavit Carolus Gottlob Kühn, Leipzig, Cnobloch, 1827, vol. 13, book 10.

in mesenchymal tissues. The factors involved in the deposition of urates are unknown. Since deposits of sodium urate rarely occur in other conditions with a concomitant hyperuricemia, local factors were incriminated for their development in gout. It was maintained that urate crystals precipitate in traumatized parts of the body and in such parts "as are remotest from the Heart" (such as toe and margin of the ear), and "through which the Liquids flow the most difficultly" (cartilage, tendons and ligaments).[12] However, the deposition of urates in the tissues cannot be attributed solely to these factors, because blood with a high urate content flows sluggishly in the same parts of the body in conditions other than gout without production of urate deposits. On the other hand, tophi are not uncommon in regions not exposed to trauma.

Tophi most frequently develop in the cartilages of the ears, in olecranal and prepatellar bursae and in and about peripheral joints. They occur less often in the connective tissue of the cutis and subcutis. Sodium urate crystals are often deposited in the interstitial tissue of the kidneys and also in the renal calices and pelves, where they form gravel or calculi.[39] In the joints the urate crystals may invoke changes similar to those prevailing in rheumatoid arthritis and osteoarthritis. Intra-articular tissue reactions as well as periarticular tophi and fibrotic changes may restrict function of the joint and cause unsightly deformities. Tophi are painless; they become painful when they interfere with motion of the joint or during acute exacerbations. Tophi may ulcerate, permitting the stones to peep out like "crab's eyes." Under the microscope, the chalky substance from a broken-down or needled tophus reveals the characteristically needle-shaped and colorless sodium urate crystals. The chemical nature of the "chalk" may also be verified by the murexide test. Microscopic examination and chemical tests are necessary to differentiate true tophi from Heberden's nodes, from calcium deposits, from the nodular swellings occurring in rheumatic fever, rheumatoid arthritis and fibrositis and from gangliomas and sebaceous cysts.

Palpable or visible tophi appear in about 50 per cent of all cases of gout. Infrequent in early gout, they are rather common in advanced gout. Since tophi generally develop eight or ten years after the clinical onset of the disease, one must not hesitate to diagnose presumptive gout in their absence if other evidence present justifies the diagnosis. Sodium urate crystals may be deposited in bone and replace osseous tissue. In roentgenograms, the osseous tophi are revealed as punched-out areas at or near articular margins. Huber,[40] in 1896, was the first to describe the specific roentgenographic features of gout, namely, sharply defined circular or oval areas of diminished density located in the distal ends of the phalanges of the feet and hands. He regarded them as cavities filled with urate crystals.

Roentgen evidence of osseous tophi is seldom discernible in the early years of gout; it was absent even in patients who had had symptoms of the disease for twenty-five or thirty years.[20] Hence, normal roentgenograms do not rule out gout. Moreover, roentgenographic evidence indicative of erosion of bone can also be obtained in various other diseases, a circumstance which further detracts from the value of roentgen examination in gout. Punched-out areas may be seen

39. Urate gravel and stones were called urinary tophi by Hench. However, in gouty persons urate gravel and stones precipitate from urine the urate content of which usually is below the normal level, whereas true tophi precipitate from blood and other body fluids having an increased urate concentration.

40. Huber: Zur Verwerthung der Röntgen-Strahlen im Gebiete der Medicin, Deutsche med. Wchnschr. **22**:182-184 (March 19) 1896.

in rheumatoid and focal arthritis, osteoarthritis, lupus pernio, cystic disease of the bones, multiple chondromas and myelomas, Schüller-Christian syndrome, syphilis, tuberculosis and yaws.

On the other hand, roentgen examination may furnish valuable information concerning prognosis of surgical treatment for gout. For instance, the bones of hands deformed by chronic arthritis and tophi may have suffered extensive damage. If roentgenography is not resorted to in such cases, the surgical removal of tophi, which, instead of the wasted bones, form the supporting frame of the hand, may render wholly useless an efficient though much deformed hand.

The most important milestone in the treatment of gout is the introduction of Colchicum autumnale,[41] or meadow saffron, in 1763, by Baron Anton von Störck,[42] physician to the Empress Maria Theresa. Prior to that time, this perennial plant was either unknown in many parts of Europe[43] or was in ill repute possibly because Dioscorides,[44] in the first century A. D., claimed that the plant was poisonous, causing death by suffocation. Baron von Störck,[42] however, demonstrated that small amounts of colchicum can be given with impunity. He stressed the drug's analgesic action for articular pains and its diuretic properties. Quacks were quick to make capital of von Störck's discovery. They flooded the market with "gout specifics"[45] (eau médicinal de Husson, liqueur antigoutteux du Docteur Laville, Reynold's specific, Albert's remedy, Want's medicinal water, etc.), many of which are still on the market and are the choice of some physicians and a large number of persons with gout. Benjamin Franklin is credited with having been the first to introduce colchicum into this country.[46]

Colchicum was known to Byzantine physicians (fifth, sixth and seventh centuries A. D.) under the name of hermodactyl (finger of Hermes).[6] It has also been called *amina articulorum* (soul of the joints). A prescription[47] of Jacobus Psychrestus, a Constantinople physician of the fifth century A. D., has been preserved for posterity by the famous Byzantine physician, Alexander of Tralles[48] (525-605 A. D.), who, like Psychrestus and Aetius[49] (sixth century) before him and Paulus Aegineta[50] (625-690 A. D.) after him, employed hermodactyl for painful articular attacks. These early physicians were familiar with the dangerous effects of the drug; they felt that it also had properties other than

41. The name colchicum originates from Colchis, an ancient district of Asia Minor.

42. Störck, A.: An Essay on the Use and Effects of the Root of the Colchicum Autumnale, or Meadow Saffron, translated from the Latin, London, T. Becket, & P. A. De Hondt, 1764.

43. Neither hermodactyl nor colchicum is mentioned among more than fifty remedies recommended for the treatment of gout by Nicholas Culpeper in 1681 (The English Physician Enlarged, London, G. Sawbridge, 1681).

44. Dioscorides Anazarbeus (Pedacius): Arzneimittellehre in fünf Büchern, translated into German by J. Berendes, Stuttgart, F. Enke, 1902, book 4.

45. Scudamore, C.: A Treatise on the Nature and Cure of Gout and Rheumatism, Including General Considerations on Morbid States of the Digestive Organs: Some Remarks on Regimen, and Practical Observations on Gravel, ed. 3, Philadelphia, E. Earle, 1819.

46. Schnitker, M. A.: A History of the Treatment of Gout, Bull. Inst. Hist. Med. 4: 89-120 (Feb.) 1936.

47. Hermodactyl, 4 scruples; scammony, 2 scruples. To drink with lukewarm water after the patient has been prepared by a good regimen.

48. Aiexander (Trallianus): Medici libri duodecim, Graeci et Latini . . . Io. Guinterio Andernaco interprete et emendatore. Adiectae sunt per eundem uariae exemplarium lectionis observationes, cum Jacobi Goupyli castigationibus, Basel, per Henricum Petrum, 1556.

49. Aetius Amidenus (Antiochemus): Libri XVI, Basel, in off. Frob. 1533-1535, sermo duodecimus.

50. Paulus Aegineta: Opus de re medica, nunc primum integrum latinitate donatum, per Joannem Guinterium Andernacum, Paris, apud S. Colinaeum, 1532, book 3.

purgative. As yet physicians are unable to explain the striking action of colchicum in the acute gouty attack. It does not act as a diuretic; it has no effect on the metabolism of purine bodies; it has no influence on the kidneys; it does not increase excretion of urates or decrease the urate content of the blood. Colchicum cannot be regarded as an analgesic, because it fails to influence the pain of a nongouty origin.

Colchicum should be administered with great caution or not at all to the old and feeble or to those who suffer from disturbance of the kidneys, heart, liver [51] or gastrointestinal tract. Colchicine, the alkaloid and active principle of Colchicum autumnale, isolated by Pelletier and Caventou [52] in 1820, is the substance preferred for the treatment of gout because its potency is constant, in contrast to that of the wine and of the tincture of colchicum, which deteriorate on standing. A saline purgative such as magnesium sulfate or sodium sulfate (½ to 1 ounce [15 to 30 Gm.]) should usher in the treatment of an acute attack of gout. The treatment is continued, with ingestion of 2 colchicine pills, 1/120 grain (0.5 mg.) each, followed hourly or every two hours by 1 pill. Patients who are being treated for the first time and whose tolerance for colchicine is unknown should be watched carefully. It is not necessary to produce nausea or purgation to obtain full therapeutic benefit with colchicine; nausea, vomiting and diarrhea indicate, rather, overdosage, and the administration of the drug should be stopped at once. The diarrhea is treated with codeine, camphorated tincture of opium or bismuth subnitrate. Patients who are warned by prodromes of an impending attack may prevent or abort it by promptly taking a few colchicine tablets. Frequent premonitory symptoms are: headache, vertigo, nausea, dyspepsia, gastrointestinal distress, mental depression, nervous irritability, nocturia and euphoria. It has been reported recently that gout cycles consisting of suppression of sweating, polyuria and gain in body weight, correlated perhaps with a fall in barometric pressure, may precede acute gouty attacks.[32]

Although, in general, colchicine is believed to be highly effective only in the acute gouty attack, there are physicians [53] who advocate its prophylactic use in the asymptomatic periods between attacks. One colchicine pill after meals for one week every four weeks,[21a] or for two or three days each week [32] has been recommended. It is said [54] that colchicomania develops in patients who take the drug too frequently. Such patients become tolerant to the drug, the dose of which must continually be increased for effectiveness. Finally, the frequency, severity and duration of the acute attacks increase. Personally, I have not encountered untoward effects from the prolonged administration of colchicum.

Fifteen centuries elapsed after Jacobus Psychrestus prescribed hermodactyl for his patients in Constantinople before a new milestone was set up in the treatment of gout. In 1908, Nicolaier and Dohrn [55] reported that cinchophen (introduced under the proprietary name atophan) increases the urinary output of urate

51. Scheifley, C. H., and Higgins, G. M.: The Effect of the Administration of Colchicine After Partial Removal of the Liver, Proc. Staff Meet., Mayo Clin. **15**:536 (Aug. 21) 1940.

52. Pelletier, P. J., and Caventou, J. B.: Examen chimique de plusiers végétaux de la famille des colchicéés et du principe actif qu'ils renferment, Ann. de chim. et phys. **14**:69, 1820.

53. Cohen.[21a] Talbott and others.[32]

54. Boulin, R.: Le colcique et la goutte, Progrès méd. **67**:585-588 (April 29) 1939.

55. Nicolaier, A., and Dohrn, M.: Ueber Wirkung von Chinolincarbonsäuren und ihrer Derivate auf die Ausscheidung von Harnsäure, Deutsches Arch. f. klin. Med. **93**:331-335 (June) 1908.

while lowering its level in the blood. In 1911, Weintraud [56] employed the drug in the treatment of gout and found that significant relief followed its use in acute attacks. He stated the belief that the action of cinchophen was more effective than that of colchicum. The exact mechanism of the pharmacologic action is not clear. It has been suggested that cinchophen enhances excretion of urates by direct action on the kidneys [56] or through the nerves controlling renal function,[56] especially through the true sympathetic.[34] Depression of reabsorption of urates by the renal tubular epithelium is another explanation offered.[36b] However, as yet it has not been proved that the uricosuric action of cinchophen is actually responsible for its therapeutic effect in gout. In addition, cinchophen has antipyretic and analgesic properties.

In acute attacks, cinchophen is given for two or three consecutive days in amounts of 7½ grains (0.48 Gm.) three, four or more times a day. After an interval of from two to four days, administration of the drug may be repeated. To prevent the precipitation of urates as gravel or stones because of the acid reaction of the urine, ingestion of cinchophen should be followed by ingestion of alkaline waters or alkaline powders (potassium citrate, sodium bicarbonate). These render the urine alkaline, in which urates are more soluble. In addition, a liberal intake of fluids and carbohydrates should be insisted on during administration of cinchophen.

It must be kept in mind that cinchophen and its derivatives, such as neocinchophen, do not cure gout; furthermore, the relief from pain in acute attacks is not so dramatic and complete as with colchicum. Moreover, cinchophen is known to cause severe and even fatal liver poisoning.[57] When toxic effects develop, such as anorexia, nausea, dyspepsia, gastrointestinal upsets, jaundice, pruritus and urticaria, administration of the drug should be stopped at once. Signs of cinchophen intoxication may first appear long after the administration of the drug was suspended.[57] Because of its toxicity and because there is no safe method of administration, many physicians do not use cinchophen at all. Others [14] feel that the risk from the drug is less than the danger to the patient from the grave renal and vascular complications of gout. Under no circumstances should cinchophen be given uninterruptedly; there should be an intermission of four to five days between courses.[58] The intermittent use of cinchophen is advocated especially in the interparoxysmal periods to avert acute attacks and to prevent or delay the development of complications and of chronic arthritis. In the intervals between acute attacks, cinchophen may be given in doses of 15 grains (1 Gm.) twice a day, one day each week.[58]

From the procession of milestones one point clearly emerges, namely, that gout is still the "physicians' shame," *opprobrium medicorum*, as Daniel Sennert [23] in the sixteenth century put it. Although many theories have been advanced, large in scale and concept, no one as yet even knows the cause of the hyperuricemia present in persons with gout; no one knows the cause of retention of urates by

56. Weintraud, W.: Die Behandlung der Gicht mit Phenylchinolincarbonsaeure (Atophan) nebst Bemerkungen ueber die diaetetische Therapie der Krankheit, Therap. d. Gegenw. **13**:97-105 (March) 1911; Weitere klinische Erfahrungen mit Atophan nebst Bemerkungen über Gicht und Harnsäure Diathese, Therap. Monatsh. **26**:21-29 (Jan.) 1912.

57. Palmer, W. L., and Woodall, P. S.: Cincophen—Is There a Safe Method of Administration? J. A. M. A. **107**:760-764 (Sept. 5) 1936. Palmer, W. L.; Woodall, P. S., and Wang, K. C.: Cincophen and Toxic Necrosis of Liver: Survey of Problem, Tr. A. Am. Physicians **51**:381-393, 1936.

58. Graham, G.: Gout, in Price, F. W.: A Textbook of the Practice of Medicine, ed. 5, London, Oxford University Press, 1937.

the body tissues and fluids or the cause of the precipitation of sodium urate into the tissues. Since the nature of the basic disturbance of gout is unknown, it is not surprising that as yet no means has been evolved to treat gouty dyscrasia. On the other hand, it seems that perpetual vigilance, adherence to a regimen of hygiene and diet of tried value and wise use of the effective drugs available can to a certain extent alter the clinical course of the disease and retard its progress. However, it appears that, despite the institution of best therapeutic measures, once gout has established itself in a person "the disease sticks to him until death" (Aretaeus, second and third centuries A. D.)[59]

135 West Seventy-Ninth Street.

59. Aretaeus (Cappadox): The Extant Works, edited and translated by Francis Adams, London, The Sydenham Society, 1856.

Recently a new method of approach to the understanding and treatment of gout has been offered. The clinical association of blood dyscrasias and gout prompted Davis (Davis, J. S.: The Liver an Etiological and Therapeutic Factor in Certain Types of Blood Disease and in Gout and Gouty Arthritis, J. A. M. A. **117**:1648-1649 [Nov. 8] 1941) to assume a possible etiologic connection between gout and a disturbance in hepatic function. He reported gratifying therapeutic results in cases of chronic gouty arthritis and tophaceous gout by injecting a "full complement" liver extract (campolon) which is not heated in preparation and from which purine bodies and proteins are removed.

Progress in Internal Medicine

INFECTIOUS DISEASES

NINTH ANNUAL REVIEW OF SIGNIFICANT PUBLICATIONS

HOBART A. REIMANN, M.D.
PHILADELPHIA

Judging by the length of this review as compared with the reviews of previous years, and by the number of papers referred to, the war up to now has not greatly interfered with the progress of the study of infectious diseases. Nor has there as yet been as great a change as expected in the trend of interest to problems of infectious diseases in special relation to the war. In the next year or two, however, more change may be anticipated in the quantity and in the nature of published investigations. Evidence of curtailment of medical research is apparent, for example, in the thinness of recent issues of the *Proceedings of the Society of Experimental Biology and Medicine* and in the cancellation of meetings of numerous other scientific societies.

In spite of the war and either as the result of the application of specific and general prophylactic and therapeutic measures or because of a change in the nature of the diseases, the death rates for scarlet fever, whooping cough, diphtheria, influenza, pneumonia, tuberculosis, typhoid fever, appendicitis and puerperal fever in 1942 have reached the lowest levels ever recorded by a large life insurance company.[1] Most striking is the reduction by 55 per cent of the mortality from the various types of pneumonia from 1938 to 1942. In the ten years prior to 1938, the year in which sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was first used, the death rate never fell below 79 per hundred thousand, but by 1942 the rate had dropped to 32 per hundred thousand. According to editorial comment[1a] reviewing the evidence at hand, it is pleasing to learn that there are at present insurmountable difficulties for the successful use of infectious agents as effective weapons of warfare.

CHEMOTHERAPY

Attempts to discover why the sulfonamide compounds exert a bacteriostatic effect and why certain bacteria are resistant to this effect continue to be made in chemotherapeutic research. In regard to the first problem Davis and Wood[2] point out a correlation between the bacteriostatic power and the protein-binding ability of seven commonly used sulfonamide compounds. The results reported support the current ideas that bacteriostasis depends on specific inhibition of an enzymatic reaction involving paraaminobenzoic acid and that enzymes are protein in nature and inhibition of their action involves some form of chemical interaction between the inhibitor and the enzyme. The authors suggest that the anionic species of the molecule of the sulfonamide compound is the active factor in the mechanism of bacteriostasis.

From the Jefferson Medical College and Hospital.

1. Excellent Health Record of a War Year, Statist. Bull. Metrop. Life Insur. Co. **23**:1-3 (July) 1942.

1a. Feasibility of Bacterial Warfare, editorial, J. A. M. A. **122**:810-811 (July 17) 1943.

2. Davis, B. D., and Wood, W. B.: Studies in Antibacterial Action of Sulfonamide Drugs: III. Correlation of Drug Activity with Binding to Plasma Proteins, Proc. Soc. Exper. Biol. & Med. **51**:283-285 (Nov.) 1942.

An increase in the amount of paraaminobenzoic acid is supposedly one of the chief causes of the resistance to the action of sulfonamide compounds, but this could not be proved until a method was devised by which that substance in cultures of bacteria could be detected and measured. By applying a new technic to cultures of certain staphylococci that were resistant to sulfonamide compounds, Landy and his associates [3] have shown that this was so. At least, the resistant staphylococci make seventy times as much paraaminobenzoic acid in a synthetic medium as do parent drug-sensitive strains of the same bacteria. Drug-fast staphylococci elaborate much more paraaminobenzoic acid than do other varieties of bacteria tested, and evidence suggests that the ability to produce these large amounts is permanent. On the other hand, the resistant strains of Escherichia coli, Vibrio cholerae, Salmonella dysenteriae and Diplococcus pneumoniae produced no more demonstrable paraaminobenzoic acid than did their parent drug-sensitive forms. Some other "antisulfonamide metabolite" or proliferative coenzyme may eventually be discovered to account for the resistance of drug-fast bacteria of these varieties to the action of the sulfonamide compounds.

If the suggested factors alone are responsible for the development of resistance to the sulfonamide compounds, it should be possible to overcome them by some means. With this in mind, a group of investigators [4] succeeded in neutralizing the action of paraaminobenzoic acid and of methionine with urea. The addition of urea inhibited the growth of the resistant staphylococci in a concentration of sodium sulfathiazole (sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole), which alone was ineffective, thus overcoming their drug-fastness. It is hoped that this innovation in chemotherapy will prove to be effective clinically. Another way to deal with drug-fast types of bacteria, at least with some of them, is to use penicillin (a filtrate of a broth culture of Penicillium notatum), to which they are sensitive. Unfortunately, according to McKee and Houck,[5] pneumococci, staphylococci and hemolytic streptococci may become penicillin fast. In this case, unlike the bacteria resistant to sulfonamide compounds, they lose virulence, according to one report.[6] Their virulence could not be restored by repeated passage in animals.

According to McKinney and Mellon,[7] pneumococci which become resistant to sulfonamide compounds are intermediate variants of the parent drug-sensitive form. The variant forms are not included among the usual M, S and R culture phases, which McLeod several years ago showed to play no part in the matter.

Another chemotherapeutic agent, propamidine (4, 4'-diamidinodiphenoxypropane dihydrochloride), was found to be bacteriostatic for staphylococci.[8] The

3. Landy, M., and Dicken, D. M.: A Microbiological Method for the Determination of P-Aminobenzoic Acid, J. Biol. Chem. **146**:109-114 (Nov.) 1942. Landy, M.; Larkum, N. W.; Oswald, E. J., and Streightoff, F.: Increased Synthesis of P-Aminobenzoic Acid Associated with the Development of Sulfonamide Resistance in Staphylococcus Aureus, Science **97**:265-267 (March 19) 1943.

4. Tsuchiya, H. M.; Tenenberg, D. J.; Strakosch, E. A., and Clark, W. G.: In Vitro Effect of Urea-Sulfathiazole Combination on Sulfathiazole-Resistant Staphylococci, Proc. Soc. Exper. Biol. & Med. **51**:245-247 (Nov.) 1942. Tenenberg, D. J.; Tsuchiya, H. M.; Clark, W. G., and Strakosch, E. A.: In Vitro Effect of Sulfonamides Plus Urea on Escherichia Coli in Presence of Para-Aminobenzoic Acid, ibid. **51**:247-249 (Nov.) 1942.

5. McKee, C. M., and Houck, C. L.: Induced Penicillin Resistance in a Pneumococcus Type III Culture, Federation Proc. **2**:100 (March 16) 1943.

6. McKee, C. M., and Rake, G.: Activity of Penicillin Against Strains of Pneumococci Resistant to Sulfonamide Drugs, Proc. Soc. Exper. Biol. & Med. **51**:275-278 (Nov.) 1942.

7. McKinney, R. A., and Mellon, R. R.: Dissociative Aspects of the Bacteriostatic Action of Sulfonamide Compounds, J. Infect. Dis. **68**:233-245 (May-June) 1941.

8. Thrower, W. R., and Valentine, F. C. O.: Propamidine in Chronic Wound Sepsis, Lancet **1**:133-136 (Jan. 30) 1943.

activity of this substance is not inhibited by paraaminobenzoic acid or by pus. It appears to be useful in treatment when applied to superficial infections.

Chemotherapy in Infections of the Respiratory Tract.—The results of treating 1,635 adults for pneumococcic pneumonia with sulfonamide compounds are reported by Flippin and his co-workers.[9] Sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) is at present the drug of choice. The mortality rate for these patients was about 10 per cent, compared with 40 per cent for 1,900 patients with pneumonia in the years just before sulfonamide compounds became available. In the discussion of this report, Rumreich cautions against the indiscriminate use of sulfonamide compounds in treating forms of pneumonia not amenable to chemotherapy. An accurate clinical and bacteriologic diagnosis should be made in each case to guide intelligent therapy. Experiments with a new compound, sulfamethyldiazine (sulfamerizine), are in progress. The drug is as effective as sulfadiazine and is absorbed more rapidly.

Dowling and his associates [10] find that giving only 2 Gm. of sulfadiazine initially and 0.5 Gm. every four hours thereafter, in other words about half the usual amount, is just as satisfactory as far as the mortality rate and the incidence of complications are concerned. However, in those receiving the smaller doses, the duration of the disease was somewhat longer, and the incidence of spread to other lobes and of relapse, higher.

Finland [11] reviews information concerning the use of chemotherapy in the treatment of bacteremia. Dick [12] reported recovery in a case of subacute bacterial endocarditis six weeks after the administration of 40 Gm. (!) of sodium sulfadiazine in one dose. Temporary suppression of urine occurred. The patient died a few months later. Others who have tried this enormous dose have not had good results therefrom.

In reference to the unwise use of the sulfonamide compounds for minor infections of the respiratory tract, Spink [13] points out that chemotherapy should not be used for this group of infections except in (1) patients with severe infections actually caused by the hemolytic streptococcus, (2) patients with colds who are known to have cardiac valvular defects, to forestall endocarditis, and (3) obstetric patients who have contracted infection of the respiratory tract at or near term. It is his practice to give sulfadiazine for at least forty-eight hours to every patient having evidence of pneumonia of any kind, but if at the end of that time the cause of the disease is undetermined and if no improvement has occurred, chemotherapy is stopped. I do not agree wholly with this plan, feeling that in the majority of cases of pneumonia one can decide at the outset or soon after whether or not chemotherapy should be used.[14] In the season of 1942-1943, at least, most of the patients with pneumonia whom I observed had the atypical (viral) type, and in only a few cases, in which the diagnosis was doubtful, was chemotherapy used. The mortality among these patients was nil whether treatment was given or not. In a controlled

9. Flippin, H. F.; Schwartz, L., and Domm, A. H.: Modern Treatment of Pneumococcic Pneumonia, J. A. M. A. **121**:230-236 (Jan. 23) 1943.

10. Dowling, H. F.; Hartman, C. R.; Feldman, H. A., and Jenkins, F. A.: The Comparative Value of High and Low Doses of Sulfadiazine in the Treatment of Pneumococcic Pneumonia, Am. J. M. Sc. **205**:197-203 (Feb.) 1943.

11. Finland, M.: Chemotherapy in the Bacteremias, Connecticut M. J. **7**:92-100 (Feb.) 1943.

12. Dick, G. F.: Subacute Bacterial Endocarditis: Recovery Following Intravenous Sodium Sulfadiazine, J. A. M. A. **120**:24-25 (Sept. 5) 1942.

13. Spink, W. W.: The Use and Abuse of Chemotherapy, Minnesota Med. **24**:988-990 (Dec.) 1942.

14. Indiscriminate Sulfonamide Therapy in Mild Infections of the Respiratory Tract, editorial, Pennsylvania M. J. **46**:719-720 (April) 1943.

study [14a] of 670 cases of infection of the respiratory tract no significant difference was observed in the duration of sickness among those given sulfadiazine as compared with control patients not receiving the drug. Pneumonia occurred equally in both groups. According to Robertson,[15] the possibility of preventing pneumonia with sulfonamide compounds does not seem hopeful in view of the failure of experimental attempts at prevention. In animals, at least, chemotherapy was unexpectedly much less effective if given before than if given after the disease had begun. Furthermore, the low incidence of pneumonia in recent epidemics of mild infection of the respiratory tract does not justify the use of chemoprophylaxis even though physicians had evidence that pneumonia could be prevented by this means. If bacterial pneumonia does occur, it can be satisfactorily treated as it arises. Conditions, however, may change, and then it may be justifiable to use chemoprophylaxis generally. For example, in the event of a large outbreak of influenza or related disease in which secondary bacterial invasion occurs as it did in 1918, there may be no time or opportunity for careful study and selection of cases for treatment.

Chemotherapy in Other Infections.—Sulfadiazine, because of its low toxicity in comparison with its relatives, is at present the drug of choice in the treatment of hemolytic streptococcic, gonococcic and staphylococcic infections and of various acute bacterial meningitides.[16] In line with current pessimism as to the relative ineffectiveness of chemotherapy for staphylococcic infections, discussed in last year's review,[17] Butler and Valentine [18] state that sulfathiazole is of little value in the treatment of patients with septicemia, and most patients with only a few cocci in their blood recover without it. They believe it should be given nevertheless if visceral involvement occurs, even with light bacteremia. Penicillin may eventually prove to be more useful.

In a study [19] of the value of sulfathiazole in chemoprophylaxis against gonorrhea, the drug was given to a group of Negro soldiers before and after they went on leave. A much larger group of untreated Negroes served as a control. A phenomenal disappearance of gonorrhea and chancroid was reported for the treated group. After chemoprophylaxis the proportion contracting gonorrhea dropped from 171 per thousand to 8 per thousand, and the proportion presenting chancroid from 52 to 6. Admittedly this method seems to be successful, but the risks involved if it is used on a larger scale are as yet unknown. Besides, the profoundly important social implications of such a measure are not mentioned. Serious questions arise as to the frequency of "healthy carriers" in whom symptoms do not occur among persons so treated and as to the possibility under these circumstances of disease being spread even more, to say nothing of the moral effects of the removal of the fear of infection.

14a. Rusk, H. A., and van Ravenswaay, A. C.: Sulfadiazine in Respiratory Tract Infections: Its Value in Treatment During the Winter of 1942-1943 at Jefferson Barracks, J. A. M. A. **122**:495-496 (June 19) 1943.

15. Robertson, O. H.: Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention, Ann. Int. Med. **18**:1-14 (Jan.) 1943.

16. Finland, M.; Peterson, O. L., and Goodwin, R. A.: Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, Ann. Int. Med. **17**:920-934 (Dec.) 1942.

17. Reimann, H. A.: Infectious Diseases: A Review of Significant Publications in 1941-1942, Arch. Int. Med. **70**:132-177 (July) 1942.

18. Butler, E. C. B., and Valentine, F. C. O.: Further Observations on Acute Staphylococcal Infections, Lancet **1**:194-197 (Feb. 13) 1943.

19. Loveless, J. A., and Denton, W.: The Oral Use of Sulfathiazole as a Prophylaxis for Gonorrhea, J. A. M. A. **121**:827-828 (March 13) 1943.

In a sort of review of progress in the chemotherapy of tuberculosis, Smith and his associates [20] show that a number of sulfonamide compounds have an inhibiting effect on the growth of tubercle bacilli. The mortality rate in a group of infected animals was reduced from 81 to 44 per cent with promin (a glucoside derivative of 4,4'-diaminophenylsulfone) and to 56 with related drugs. Attempts are being made to produce more effective and less toxic drugs. Another short summary of the problem appears elsewhere,[21] in which it is pointed out that as yet no drugs other than the sulfonamide compounds have been found efficacious in the treatment of tuberculosis in animals or man. Sulfanilamide is of no value in the treatment of leprosy but has proved to be effective in controlling the secondary or complicating infections.[22] Eosinophilia often occurs in lepers treated with sulfanilamide. As to the treatment of leprosy in rats with sulfonamide compounds, conflicting results have been reported. According to Krakower and his associates,[23] sulfanilamide and sulfathiazole were bacteriostatic for a mouse strain of Mycobacterium leprae. Growth and dissemination of the lepromas were inhibited while the rats were under treatment, but relapse occurred when therapy was stopped. There was no indication that the bacilli residing in the lesions were killed by the drugs.

A careful analysis of patients with paratyphoid B fever failed to reveal any evidence of the effectiveness of sulfaguanidine in treatment in the acute, the convalescent or the carrier stage.[24] Although sulfadiazine reduced the number of typhoid bacilli in the intestine, the chronic carrier state was not terminated.[24a] The sulfonamide compounds are of no value in the treatment of typhoid fever either.[24b]

According to a report of experience in Africa, sulfapyridine acts as a specific for the bubonic form of plague.[25] Of 547 patients, 345 died. All but 2 of the 131 pneumonic or septicemic patients died. Since most of the patients with the bubonic form who recovered did so by the second or third day, one wonders how much chemotherapy had to do with it, since they were the ones with the mildest infection. Control studies of cases of bubonic plague of similar severity are essential before the value of the drug in the treatment of this disease can be judged.

As in studies reported previously, sulfanilamide had no effect on the "toxic phase" of smallpox, but the later phase, associated with pyogenic bacteria, was modified in some cases.[26]

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20. Smith, M. L.; Emmart, E. W., and Westfall, B. B.: The Action of Certain Sulfonamides, Sulfones and Related Phosphorus Compounds in Experimental Tuberculosis, J. Pharmacol. & Exper. Therap. **74**:163-171 (Feb.) 1942.

21. Sulfone Compounds for Pulmonary Tuberculosis, Queries and Minor Notes, J. A. M. A. **121**:798 (March 6) 1943.

22. Faget, G. H.; Johansen, F. A., and Ross, H.: Sulfanilamide in the Treatment of Leprosy, Pub. Health Rep. **57**:1892-1899 (Dec. 11) 1942.

23. Krakower, C.; Morales-Otero, P., and Axtmayer, J. H.: The Effect of Sulfanilamide on Experimental Leprosy, J. Infect. Dis. **72**:1-10 (Jan.-Feb.) 1943.

24. Scott, T. F. M.; Beeson, P. B., and Hawley, W. L.: Paratyphoid B Infection: The Ineffectiveness of Sulphaguanidine, Lancet **1**:487-490 (April 17) 1943.

24a. Hardy, A. V.: The Bacteriostatic Action of Sulfadiazine on E. Typhosa in Carriers and Cases, Pub. Health Rep. **58**:833-839 (May 28) 1943.

24b. Hoagland, R. J.: The Treatment of Typhoid: The Ineffectiveness of Sulfathiazole and Immune Serum, J. A. M. A. **122**:153-156 (July 3) 1943.

25. Plum, D.: Plague Epidemic in Nairobi, with Special Reference to Place Incidence and Treatment, East African M. J. **19**:3-9 (April) 1942.

26. Wilkinson, P. B.: Sulfanilamide in Treatment of Smallpox: Review of One Hundred and Three Cases, Lancet **2**:67-68 (July 18) 1942.

After treating 12 patients with nonspecific ulcerative colitis, Kirsner and his collaborators [27] report no beneficial effect from sulfaguanidine (sulfanilyguanidine). The drug had no advantage over related ones in the treatment of lymphogranuloma venereum of the rectum. The bacterial flora, however, was greatly altered from predominantly coliform to gram-positive bacteria. The change of flora interferes with the normal putrefactive bacteria, helpful in digestion and nutrition, with the result that there was a loss of weight in the test animals. Normal growth may be maintained under these circumstances by the administration of either liver extract or folic acid.[28] Contrary to most reports, as discussed on page 403, the authors [27] noted only slight temporary benefit in 2 cases of infection with Bacillus dysenteriae Flexner.

The value of sulfonamide compounds in the therapy of mycotic infections is as yet unknown. Numerous reports of single cases in which recovery took place during therapy are on record but are of little value without controlled observation.[29] Here again the antibiotic agents may be more helpful. Sulfapyridine had no effect on typhus fever in one study,[30] and sulfadiazine failed to control infectious mononucleosis in another.[31] While sulfathiazole and sulfapyridine had no effect on the protozoan Toxoplasma in vitro, they completely inhibited its growth in infected mice when given orally.[32] In most other infections the reverse usually occurs.

From the first comprehensive study to ascertain how many people actually have died from the effects of sulfonamide compounds, Sutliff and his associates [33] conclude that the small number of such persons warrants the continued use of the drugs in the usual dosages for the diseases in which they are of value. The benefits derived outweigh the risk involved. They encountered the usual difficulties in their search because of the incomplete or unsatisfactory records of many cases. For example, only one death ascribed to a sulfonamide compound appeared to have been noted among 685 deaths in cases of pneumonia in New York, but a more careful perusal of the statistics showed that the one death from toxicity occurred among 161. As near as one can judge, 1 death is caused by a sulfonamide compound in every 1,600 cases of pneumonia in which such drugs are used. It is often difficult and at times impossible to judge whether death is caused by the treatment, by the disease or by the combination of the two.

In discussing this paper, Long estimates that about 1,700 tons of sulfonamide compounds were made in the United States in 1941 and that between 10,000,000 and 15,000,000 persons received them in some form of therapy. He points out the need for using these drugs only when they are indicated, because of the possible sensitization of a large percentage of persons who take them.

27. Kirsner, J. B.; Rodaniche, E. C., and Palmer, W. L.: Use of Sulfaguanidine in Non-Specific Ulcerative Colitis and Other Infections of the Bowel, Am. J. Digest. Dis. **9**:229-233 (July) 1942.

28. Gant, O. K.; Ransone, B.; McCoy, E., and Elvehjem, C. A.: Intestinal Flora of Rats on Purified Diets Containing Sulfonamides, Proc. Soc. Exper. Biol. & Med. **52**:276-279 (April) 1943.

29. Marshall, M., and Teed, R. W.: Torula Histolytica Meningoencephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy; Preliminary Report, J. A. M. A. **120**:527-529 (Oct. 17) 1942.

30. Donald, C., and Barker, P. B.: Louse-Borne Typhus Fever, Brit. M. J. **2**:333-335 (Sept. 19) 1942.

31. Kilham, L., and Steigman, A. J.: Infectious Mononucleosis, Lancet **2**:452-454 (Oct. 17) 1942.

32. Sabin, A. B., and Warren, J.: Therapeutic Effectiveness of Certain Sulfonamides on Infection by an Intracellular Protozoan (Toxoplasma), Proc. Soc. Exper. Biol. & Med. **51**:19-23 (Oct.) 1942.

33. Sutliff, W. D.; Helpern, M.; Griffin, G., and Brown, H.: Sulfonamide Toxicity as a Cause of Death in New York City in 1941, J. A. M. A. **121**:307-312 (Jan. 30) 1943.

Penicillin.—Encouraging results are accruing from clinical studies on the use of penicillin in treating infections. The substance as developed by British investigators is said to have several advantages over sulfonamide compounds: It is relatively nontoxic, nonhemolytic and highly soluble, and its action is not inhibited by pus or by paraaminobenzoic acid. A form of penicillin called penicillin B was recently discovered.[34] In addition to being active against gram-positive cocci, it attacks gram-negative ones as well, but it is also toxic for mice. Another compound consisting of esters of the acid of penicillin was studied by Meyer and his co-workers.[35]

Thus far in clinical use penicillin seems to be effective for infections with staphylococci, hemolytic streptococci, certain susceptible strains of pneumococci and gonococci.[35a] Unfortunately, thus far it has been of no value in the treatment of the subacute bacterial endocarditis due to Streptococcus viridans. The substance is best given intravenously in physiologic solution of sodium chloride by the continuous drip method in doses of 30,000 to 40,000 Florey, or Oxford, units a day. In 7 patients with various severe infections so treated Herrell [36] reports good results and no toxic effects, but unfortunately controls in a study like this are difficult to arrange. Penicillin was effective in treating several patients infected with gonococci which were resistant to sulfonamide compounds.[37] In my own experience, recovery occurred in a case of severe primary staphylococcic pneumonia in which 440,000 units of penicillin was given over a period of thirteen days. Penicillin was found to be effective against both pneumococci that were resistant and pneumococci that were susceptible to the action of sulfonamide compounds.[38] It must be recalled here that pneumococci may become penicillin fast. Penicillin-fast pneumococci are not resistant to sulfonamide compounds. One wonders whether a given strain of pneumococci may become resistant to both penicillin and a sulfonamide compound. In the experience of Schmidt and Sesler [39] pneumococci which become penicillin resistant retain their virulence, in contrast with the observations discussed previously. The versatility of the pneumococcus in adapting itself specifically to such diverse agents as bile, the sulfonamide compounds, penicillin and ethylhydrocupreine hydrochloride is remarkable.

By using a protamine it is possible to "sensitize" gram-negative bacteria, ordinarily not susceptible, to the action of gramicidin [40] (a crystalline substance

34. Roberts, E. C.; Cain, C. K.; Muir, R. D.; Reithel, F. J.; Gaby, W. L.; Van Bruggen, J. T.; Homan, D. M.; Katzman, P. A.; Jones, L. R., and Doisy, E. A.: Penicillin B, an Anti-Bacterial Substance from Penicillium Notatum, J. Biol. Chem. **147**:47-58 (Jan.) 1943.

35. Meyer, K.; Hobby, G., and Chaffee, E.: On Esters of Penicillin, Science **97**:205-206 (Feb. 26) 1943. Meyer, K.; Hobby, G. L., and Dawson, M. H.: The Chemotherapeutic Effect of Esters of Penicillin, Proc. Soc. Exper. Biol. & Med. **53**:100-104 (June) 1943.

35a. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387-396 (March 27) 1943. Blake, F. G., and Craige, B.: Penicillin in Suppurative Disease of the Lungs: Report of Three Cases, Yale J. Biol. & Med. **15**:507-516 (Jan.) 1943.

36. Herrell, W. E.: Further Observations on the Clinical Use of Penicillin, Proc. Staff Meet, Mayo Clin. **18**:65-76 (March 10) 1943.

37. Herrell, W. E.; Cook, E. N., and Thompson, L.: Use of Penicillin in Sulfonamide Resistant Gonorrheal Infections, J. A. M. A. **122**:289-292 (May 29) 1943.

38. Tillett, W. S.; Cambier, M. J., and Harris, W. H.: Sulfonamide-Fast Pneumococci: A Clinical Report of Two Cases of Pneumonia Together with Experimental Studies on the Effectiveness of Penicillin and Tyrothricin Against Sulfonamide-Resistant Strains, J. Clin. Investigation **22**:249-255 (March) 1943.

39. Schmidt, L. H., and Sesler, C. L.: Development of Resistance to Penicillin by Pneumococci, Proc. Soc. Exper. Biol. & Med. **52**:353-357 (April) 1943.

40. Miller, B. F.; Abrams, R.; Dorfman, A., and Klein, M.: Antibacterial Properties of Protamine and Histone, Science **96**:428-436 (Nov. 6) 1942.

isolated from soil bacilli, highly bactericidal for gram-positive micro-organisms). Methylthionine chloride and acriflavine have a similar effect in increasing the effectiveness of tyrothricin (an extract from Bacillus brevis of Dubos). It appears that other compounds, such as histone, with a relatively simple polypeptide configuration may also be found to have antibacterial properties. Protamine and histone are too toxic for therapeutic use.

In Neter's [41a] experiments both pyocyanase and zephiran (a mixture of alkyl, dimethyl and benzyl ammonium chlorides) detoxified tetanus toxin. Zephiran also delays the clotting of oxalated plasma by staphylococci and inhibits fibrinolysis by Streptococcus haemolyticus. Zephiran chloride has recently been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for listing in "New and Non-Official Remedies." [41b] It is a new disinfectant, germicidal for many pathogenic nonsporulating bacteria and fungi. Solutions of the substance have low surface tension and have detergent, keratolytic and emulsifying action. In dilutions of 1 : 1,000 to 1 : 10,000 it is used to disinfect the surface of skin and mucous membranes.

Other antibiotic substances, such as pyocyanine, synthetic hemipyocyanine and pyocyanase, have been tested.[42] Both tyrothricin and hemipyocyanine are fungistatic and may be of value in the treatment of fungous infections.

COCCIC DISEASES

Pneumococcic Pneumonia.—The death rate from pneumonia of all types in 1941-1942 decreased to the lowest rate ever recorded by a large life insurance company,[43] dropping successively from 44, 40 and 32 per hundred thousand in the past three years. The decline is not wholly due to the use of sulfonamide compounds since it had been slowly progressing for many years before and is influenced by other factors as well, but chemotherapy, introduced in 1938, almost certainly caused a sharper decline. I believed that the death rate would be even lower this year because of the great number of cases in which the pneumonia was of a benign atypical ("viral") type, but statistics show otherwise. Apparently the death rate has increased by 40 per cent over a similar period in 1943, supposedly because of fatal cases of "viral" pneumonia.[44] This is surprising since in practically all reports of series of cases of "viral" pneumonia the mortality rate is nil. Deaths said to be due to "viral" pneumonia call for reinvestigation.

According to a survey [45] of over 30,000 cases of pneumonia in the years 1938 to 1940, over three fourths were caused by pneumococci. The proportion was

41. (*a*) Neter, E.: Effect of Alkyl-Dimethyl-Benzyl-Ammonium Chlorides (Zephiran) upon Tetanus Toxin, Proc. Soc. Exper. Biol. & Med. **51**:254-256 (Nov.) 1942; Effects of Alkyl-Dimethyl-Benzyl-Ammonium Chlorides upon Plasma Coagulation by Staphylococcus and Fibrinolysis by Streptococcus, ibid. **51**:256-258 (Nov.) 1942. (*b*) New and Nonofficial Remedies, J. A. M. A. **120**:289 (Sept. 26) 1942.

42. Stokes, J. L.; Pick, R. L., and Woodward, C. R., Jr.: Antimicrobial Action of Pyocyanine, Hemipyocyanine, Pyocyanase and Tyrothricin, Proc. Soc. Exper. Biol. & Med. **51**:126-130 (Oct.) 1942.

43. Pneumonia Death Rate Lowest on Record, Statist. Bull. Metrop. Life Ins. Co. **23**:8-10 (Nov.) 1942.

44. Recent Increase in Pneumonia Mortality, Statist. Bull. Metrop. Life Insur. Co. **24**:7-9 (April) 1943.

45. Rumreich, A. S.; Shaughnessy, H. J.; Mulcahy, J. V.; Willett, J. C.; Kellogg, W. H., and Mitchell, W. C.: A Nation-Wide Study of the Bacterial Etiology of the Pneumonias, Pub. Health Rep. **58**:121-135 (Jan. 22) 1943.

reversed in 1942 in many localities where atypical ("viral") pneumonia was common. The distribution of cases according to type of pneumococci remained constant in each area investigated from year to year. In the two year period the predominant types were prevalent in the following order: I, III, VII, VIII, IV, VI, V, XIX and XIV. These types caused 75 per cent of all cases of pneumococcic pneumonia in which the type was determined. In a survey [46] of an urban population in the years 1934 to 1936 the incidence of pneumonia of all types was 5.4 per thousand persons, the average duration of disability was thirty-nine days and the case fatality rate was 17.5 per cent.

Finland [47] reviews the epidemiology of pneumococcic infection. It is clear from modern bacteriologic studies that both patients with pneumonia and carriers of pneumococci are responsible for the spread of this disease, but carriers, being more numerous, are probably the more important source of infection. The spread of disease-producing pneumococci is greatest within households, barracks or dormitories, where intimate and prolonged personal contact is favored. Although there is reason to believe that infection is usually air borne, there is, strangely enough, but little evidence to prove that it is. The problem is discussed again on page 398. Because of the knowledge now available, it is important to determine the type of the infecting pneumococci in each case whether the disease produced is pneumonia or otherwise. Each patient must be regarded as a disseminator of infection and isolated from others. Sputum, saliva, handkerchiefs, bed clothing and other articles that are likely to harbor pneumococci should be sterilized. Dusting should be carefully done.

It seems to me that the influence of mild acute infections of the respiratory tract as a precursor of pneumonia is not adequately stressed in the review. Since such infections precede from 50 to 80 per cent of cases of pneumococcic pneumonia, their prevention would seem to be the greatest single factor in controlling the incidence of pneumonia. It is generally believed that a person's liability to contract pneumococcic infection is dependent on his susceptibility to, or resistance against, the pneumococcus, and if resistance could be kept intact by preventing "colds," pneumococcic invasion and disease would not occur in many persons.

Finland [48] discusses the use of antipneumococcic serums for pneumonia caused by the higher-numbered types of pneumococci. There are now 68 recognized types and subtypes, which seems to complicate the matter greatly, but the difficulties are lessened if the antiserums are made with given types and their subtypes. In general such antiserums are just as valuable in treatment as those for the lower-numbered types if given with the same precision, and, like them, are particularly valuable for patients who are sensitive to sulfonamide compounds or for those who are infected with pneumococci that are resistant to these compounds. Because the distribution of the higher-numbered types is the same in healthy carriers as in patients with pneumonia, it is often difficult to decide whether the pneumococci found in the sputum are the cause of the pneumonia or merely reside as saprophytes in the nasopharynx. When pneumococci are present in the blood or the spinal fluid, they are almost certainly the cause of the disease. Invasiveness of the relatively less

46. Britten, R. H.: The Incidence of Pneumonia as Recorded in the National Health Survey, Pub. Health Rep. **57**:1479-1494 (Oct. 2) 1942.

47. Finland, M.: Recent Advances in the Epidemiology of Pneumococcal Infection, Medicine **21**:307-344 (Sept.) 1942.

48. Finland, M.: The Present Status of the Higher Types of Antipneumococcus Serums, J. A. M. A. **120**:1294-1307 (Dec. 19) 1942.

virulent higher-numbered types of pneumococci depends largely on lack of resistance in the host.

Faller and his associates [49] point out how unreliable statistics of pneumonia may be, even in hospital practice. In scrutinizing the records of 377 deaths ascribed to pneumonia, this disease was obviously the primary cause of death in only 35 per cent of the cases and probably not the cause in another 8 per cent. In 19 per cent there was no evidence in the records by which pneumonia could be diagnosed at all. How can one account for such a high proportion of errors? Some of the factors, according to the authors, are as follows: (1) There is a tendency to use the term "pneumonia" to satisfy legal requirements when a named cause of death is needed in an obscure case; (2) many physicians diagnose pneumonia too readily merely because of fever and pulmonary rales; (3) conditions such as pulmonary collapse or infarct are often misdiagnosed, especially in surgical cases; (4) there is often uncertainty as to whether the patient died from pneumonia or whether pneumonia developed because the patient was dying; (5) records are often poorly kept, and nomenclature is confused; (6) roentgenograms were made in only 38 per cent of cases, possibly, to cite one reason at least, because of the exorbitant charges often made for this service, and (7) attempts to discover the cause of the pneumonia bacteriologically were made in only 15 per cent of cases. The last shortcoming is most discouraging to those who have made efforts to stimulate interest in etiologic diagnosis by which accurate clinical diagnosis and rational specific therapy is guided.

Frisch and his co-workers [50] give a summary of their work concerning the value of examining sputum stained by Wright's method as a guide to prognosis and therapy in a number of similar papers in different journals. In general, regardless of the type of pneumococcus except type III, of the duration of disease before specific therapy is begun or of the presence of bacteremia, the prognosis is good and the mortality rate is 2 per cent when not more than 10 pneumococci per field are present. With 11 to 30 per field the mortality rate is 9 per cent; with 31 to 75, 30 per cent, and with a number exceeding 75 per field, 77 per cent. Chemotherapy had no appreciable effect on the fatality rate when the count was high. Antiserum in adequate doses causes prompt clumping of pneumococci in the sputum, while the sulfonamide compounds reduce the numbers present within twelve to thirty-six hours unless the pneumococci are drug resistant. Matters are different when pneumonia is caused by type III pneumococcus because of the large amount of capsular polysaccharide made by this bacterium. In stained smears of sputum, the polysaccharide appears as a reticulum. When "reticulation" is present, the mortality rate is 79 per cent, compared with 7 per cent when it is absent. In patients with "reticulated" sputum sulfathiazole lowered the mortality rate from 100 to 67 per cent. Antiserum is of no avail and should not be used unless the pneumococci are drug resistant.

Frisch's test, while valuable, serves as an indication among others of the prognosis and as a guide to therapy. It cannot be applied, of course, in the occasional

49. Faller, C. P.; Quickel, K. E., and Smith, C. W.: All That Is Called Pneumonia Is Not Pneumonia: A Critical Analysis of Three Hundred and Seventy-Seven Deaths Ascribed to Pneumonia Occurring in Hospitals in Central Pennsylvania, Pennsylvania M. J. **46**:339-345 (Jan.) 1943.

50. Frisch, A. W.; Price, A. E., and Myers, G. B.: Pneumococcic Pneumonia: The Prognostic Significance of the Number of Pneumococci in the Sputum in Relation to Therapy, Bacteremia, Type, Leukocyte Count, Duration of the Disease, Age and Degree of Involvement, J. Clin. Investigation **22**:207-214 (March) 1943; Type III Pneumonia: The Prognostic Significance of Reticulation in Relation to the Number of Pneumococci in the Sputum, Therapy, Bacteremia, Leukocyte Count, Age and Degree of Involvement, ibid. **22**:215-220 (March) 1943.

case in which sputum is not raised, and it is unreliable if other complicating factors are present.

Robertson [15] summarizes his work on the genesis of pneumonia. Certain conditions are essential to cause the disease: (*a*) the implantation of pneumococci in the terminal airways either by inhalation or by aspiration of infected fluid; (*b*) the presence of a viscous medium, which prevents their rapid expulsion from this region of the lung, and (*c*) local irritation such as may be caused by mild infection of the respiratory tract. The escape of infected fluid exudate from the upper respiratory tract past the epiglottis plays a much more important role in the inception of pneumonia than does the inhalation of bacteria-laden droplets. The spread of infection within the lungs is brought about by the migration of infected thin edema fluid.

In discussing the cause of postoperative pneumonia Robertson refers to the work of Nungester and Klepser, who show how important closure of the epiglottis is in preventing aspiration of fluid. Atelectasis is also a factor in hindering the expulsion of exudate and favoring pneumonia. Pneumonia is particularly liable to occur if there is mild infection of the respiratory tract to provide the factor of irritation. Irritation, therefore, is a more decisive factor than obstruction in determining the inception of pneumonia.

Nungester and his associates [51] show that in addition to the presence of viscous material in the lungs to favor the development of pneumonia, the relative force of inspiration and expiration is also important in determining whether mucus is aspirated or expelled.

An interesting experiment was made by linking fluorescein isocyanate to the antibody of type III pneumococcus.[52] The antibody conjugate could be specifically stained in localized areas in mice infected with type III pneumococcus. The method seems to be a valuable one to demonstrate antigens in tissues, especially in investigations to determine the damage supposedly resulting from union of antigen and antibody, and perhaps in locating the sites of certain viruses.

Another unexpected antigenic relationship of pneumococci to unrelated bacilli was described in two papers.[53] Several years ago a relationship between type II pneumococci and type B Friedländer bacilli was discovered; now one learns that type VI and type XXIX pneumococci and type B Haemophilus influenzae have certain capsular antigens in common.

Other Bacterial Pneumonias.—Studies on the clinical and pathologic aspects of staphylococcic pneumonia have been published.[54] Staphylococcic pneumonia may develop in patients with influenza and may assume epidemic proportions in local areas during an epidemic of influenza. It assumes various forms and has various sequels.

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51. Nungester, W. J.; Klepser, R. G., and Kempf, A. H.: Consideration of the Respiratory Pattern as a Predisposing Factor in the Etiology of Pneumonia, J. Infect. Dis. **71**:57-60 (July-Aug.) 1942.

52. Coons, A. H.; Creech, H. J.; Jones, R. N., and Berliner, E.: The Demonstration of Pneumococcal Antigen in Tissues by the Use of Fluorescent Antibody, J. Immunol. **45**:159-170 (Nov.) 1942.

53. Neter, E.: Antigenic Relationship Between H. Influenzae Type B and Pneumococcus Type VI, Proc. Soc. Exper. Biol. & Med. **52**:289-292 (April) 1943. Zepp, H. D., and Hodes, H. L.: Antigenic Relation of Type B H. Influenzae to Type 29 and Type 6 Pneumococci, ibid. **52**: 315-317 (April) 1943.

54. Finland, M.; Peterson, O. L., and Strauss, E.: Staphylococcic Pneumonia Occurring During an Epidemic of Influenza, Arch. Int. Med. **70**:183-205 (Aug.) 1942. Wollenman, O. J. and Finland, M.: Pathology of Staphylococcal Pneumonia Complicating Clinical Influenza, Am. J. Path. **19**:23-41 (Jan.) 1943.

A case of pneumonia caused by Micrococcus tetragenus is reported.[55] A case of pneumonia was reported in which Trichomonas buccalis was thought to be the cause, but evidence therefor is doubtful.[56] The mere presence of certain microorganisms does not always indicate a causal relationship to disease. The same criticism may be applied to the alleged causative relation of Streptococcus viridans to cases of pneumonia.[56a]

Pneumococcic Meningitis.—Hodes, Smith and Ickes[57] report their results in treating patients for pneumococcic meningitis. Of 60 patients, recovery occurred in 42 per cent after treatment with sulfapyridine, sulfadiazine or sulfathiazole. Sixty-four per cent of patients over the age of 2 recovered. This percentage is much higher than that obtained by others. Twenty-nine patients received specific serum in addition, but the authors were unable to say that those who received it were aided more than those treated by chemotherapy alone.

Streptococci.—An interesting point of view in regard to infection with hemolytic streptococci is proposed by Boisvert and his associates.[58] Streptococcic infection, they believe, may be compared with tuberculosis to advantage, and the term "streptococcosis" introduced to embrace it. In both conditions, first infections and reinfections have similar characteristic peculiarities. In early infancy, for example, hemolytic streptococcic infection behaves as a subacute disease, often lasting six weeks, which may be regarded as a clinical entity called "streptococcic fever, childhood type." In later life, reinfection is more apt to cause short violent local disease like acute tonsillitis, which may be called "streptococcic fever, adult type." Scarlet fever may be a manifestation of a special allergic condition in a child who had previously had streptococcic fever.

Further analogy with tuberculosis is suggested by the carrier or latent state, designated "latent streptococcosis." A study of the records of nearly 5,000 children at the New Haven Hospital indicates that 14 per cent had "streptococcosis" and that in 25 per cent hemolytic streptococci were present in the nose, throat or elsewhere as "latent streptococcosis." In studying the authors' concept one wonders whether or not their plan may not be generalized and applied to other infectious diseases, such as those caused by pneumococci and staphylococci and perhaps those caused by certain filtrable viruses as well.

An explosive outbreak of hemolytic streptococcus sore throat occurred in a military camp in June 1942.[59] Ten per cent of 3,000 men were sick. The disease seemed to be caused by massive inoculation originating from a common source, since there was no evidence of spread from person to person. The epidemic affected nearly 200 soldiers during the first two days, after which it rapidly disappeared. Although the disease was disabling, it was seldom grave and seemed to be caused by massive infection with hemolytic streptococci of type 15, group A, rather than with a particularly virulent strain. There were few complications, but a scarlatinal rash occurred in 25. The severity was not different in those with or without

55. Tobin, W. R.: Pneumonia Caused by Micrococcus Tetragenus, J. A. M. A. **121**:41 (Jan. 2) 1943.

56. Glaubach, N., and Guller, E. J.: Pneumonia Apparently Due to Trichomonas Buccalis, J. A. M. A. **120**:280-281 (Sept. 26) 1942.

56a. Solomon, S., and Kalkstein, M.: Pneumonia Due to the Streptococcus Viridans, Am. J. M. Sc. **205**:766-770 (June) 1943.

57. Hodes, H. L.; Smith, M. H. D., and Ickes, H. J.: Sixty Cases of Pneumococcic Meningitis Treated with Sulfonamides, J. A. M. A. **121**:1334-1337 (April 24) 1943.

58. Boisvert, P. L.; Darrow, D. C.; Powers, G. F., and Trask, J. D.: Streptococcosis in Children: A Nosographic and Statistical Study, Am. J. Dis. Child. **64**:516-534 (Sept.) 1942.

59. Bloomfield, A. L., and Rantz, L. A.: An Outbreak of Streptococcic Sore Throat in a Camp, J. A. M. A. **121**:315-319 (Jan. 30) 1943.

exanthem. In no case did rheumatic fever or nephritis occur as a sequel. In incidental discussion the authors again raise the point as to whether hemolytic streptococcus tonsillitis and scarlet fever should be considered as separate diseases or not. They favor the view, as do many others, of regarding them as one disease with different manifestations but subject to the same rules of quarantine.

Extensive research in streptococcic infection was made by Rantz and his co-workers. In one report [60] they state that, of 392 strains of streptococci from all human sources except the respiratory tract, only 6.6 per cent belonged to group A and only 28 per cent were beta hemolytic; the remainder were of the viridans or nonhemolytic variety. Group A hemolytic streptococci therefore are seldom present anywhere except in the respiratory tract. Of the 392 strains, 82 per cent could be assigned to one of the Lancefield groups A, B, C, D, F, G and H. The majority were of group D, which are exceedingly resistant to the action of the sulfonamide compounds.

Hemolytic streptococci other than those of group A may cause severe infection in man.[61] Of 13 cases of septicemia, 6 were due to such organisms—4 to those of group B, 1 to those of group C and 1 to those of group D. Sulfanilamide was useful against each group except D. It is obvious that it is desirable to determine the group and the type number of all hemolytic streptococci causing infections as a guide to therapy and prognosis.

The value of each of various tests used for the determination of infection with the hemolytic streptococcus was briefly discussed.[62] The authors applied the slide agglutination method for types 1, 2, 4, 6, 9, 11, 12, 13 and 25 to the serums of 47 normal persons and compared the results with the antitoxic immunity by means of the antistreptolysin measurement. Almost one half of these persons had agglutinins for one or more types in a titer of 1:4 or less, and these had not had previous known infections with Str. haemolyticus. However, for 47 per cent of those who had had such infections the titer was 1:4 and in some cases as high as 1:8. No correlation was found between the amounts of circulating agglutinins and the amount of antistreptolysin. Among 24 patients with scarlet fever, agglutinins were demonstrated in only about one half. Agglutinins for heterologous types also developed occasionally. In 2 cases agglutinins were present at the onset of the disease, indicating that they in themselves do not confer immunity. Similar studies are in progress to determine whether the slide agglutination test will be of value in the diagnosis of rheumatic arthritis and rheumatic fever, but the authors are doubtful of its value because of the presence of antibodies in so many normal persons.

Enterococci, a group of hemolytic and nonhemolytic streptococci of Lancefield's group D, are isolated from human sources [63] other than the respiratory tract more frequently than any other streptococci. They are of low invasiveness but may be the cause of otitis media, endocarditis, peritonitis and infections of the urinary

60. Rantz, L. A.: The Serological and Biological Classification of Hemolytic and Nonhemolytic Streptococci from Human Sources, J. Infect. Dis. **71**:61-68 (July-Aug.) 1942.

61. Rantz, L. A., and Kirby, W. M. M.: Hemolytic Streptococcus Bacteremia: Report of Thirteen Cases with Special Reference to Serologic Groups of Etiologic Organisms, New England J. Med. **227**:730-733 (Nov. 12) 1942.

62. Rantz, L. A.; Kirby, W. M. M., and Jacobs, A. H.: Group A Hemolytic Streptococcus Antibodies: I. Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infections, J. Clin. Investigation **22**:411-418 (May) 1943.

63. Rantz, L. A., and Kirby, W. M. M.: Enterococcic Infections: An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, Arch. Int. Med. **71**:516-528 (April) 1943.

tract. They are exceedingly resistant to the bacteriostatic effects of sulfonamide compounds.

In another study [64] tests were performed on children before and after tonsillectomy. Children who were carriers of Str. haemolyticus were found to have an increased amount of antibody. When the carrier state was terminated by tonsillectomy, there was a constant decline in the titer of antistreptolysin within sixty days, but no consistent fall in the titer of agglutinin. Any interpretation of these results should not be oversimplified and should not be used to support the practice of routine removal of tonsils. It is probable that hemolytic streptococci may be harbored in lymphoid tissue in the respiratory tract other than the tonsils.

In a review of the subject of focal infection as it pertains to ophthalmology Woods [65] has come to the conclusion that the removal of minor and symptomless foci of infection as a cure-all for endogenous ocular disease has no place in modern practice.

Rhoads and Afremow [66] found hemolytic streptococci to be the cause of two thirds of the attacks of tonsillitis, pharyngitis, laryngitis and sinusitis in young adults. Persons who carry hemolytic streptococci in their throats or green-forming streptococci in their noses usually have active infection or are convalescent from active infection. Twenty per cent of a group of students were found to be carriers of Str. haemolyticus. Green-forming cocci, including both streptococci and pneumococci, were found in all cultures of secretions from throats and are therefore regarded as normal inhabitants of the pharynx. Carriers of hemolytic streptococci are potential sources of infection for others and perhaps ought to be quarantined. Methods such as the administration of sulfanilamide, the application of ultraviolet rays or the spraying of the throat with a solution of tyrothricin had no effect in ridding carriers of their streptococci. Spraying the throat with a solution of sodium sulfathiazole was effective in some cases.

In the experience of Colebrook and his co-workers [67] nonhemolytic streptococci were cultured from 13 patients suffering from a disease like that caused by group A hemolytic streptococci. All 13 strains reacted specifically in group A antiserum, and 11 were agglutinated by type XII antiserum. The infections caused by these 11 strains developed shortly after infections with type XII hemolytic streptococci had occurred in the wards. Both the hemolytic and the nonhemolytic type XII strains were insensitive to sulfanilamide. These observations indeed seem to add confusion and uncertainty to identifications by grouping and typing and raise the old question of the relationship between the hemolytic and the nonhemolytic forms: Are they variants of each other or may a certain strain lose and gain hemolytic ability under different conditions? In another study Orgain and Poston [68] report the presence of two or more species of bacteria in 6 patients with endocarditis. In 3 of the patients both Str. haemolyticus and Str. viridans were present; in 1, Str. haemolyticus and Streptococcus faecalis, and in the remainder, other bacteria.

64. Rantz, L. A.; Jacobs, A. H., and Kirby, W. M. M.: Group A Hemolytic Streptococcus Antibodies: II. Griffith Type Agglutinin and Antistreptolysin Titers in Carriers and Non-Carriers, J. Clin. Investigation **22**:419-423 (May) 1943.

65. Woods, A. C.: Focal Infection, Am. J. Ophth. **25**:1423-1444 (Dec.) 1942.

66. Rhoads, P. S., and Afremow, M. E.: Streptococcic and Pneumococcic Infections of the Nose and Throat in Young Adults: Incidence, Epidemiology and Clinical Features, Arch. Int. Med. **71**:443-453 (April) 1943.

67. Colebrook, L.; Elliott, S. D.; Maxted, W. R.; Morley, C. W., and Mortell, M.: Infection by Nonhemolytic Group A Streptococci, Lancet **2**:30-31 (July 11) 1942.

68. Orgain, E. S., and Poston, M. A.: Mixed Infections in Bacterial Endocarditis, Am. Heart J. **23**:823-836 (June) 1942.

An apparently successful attempt was made to classify strains of Str. viridans into specific serologic types.[69] Of 205 strains, 66 per cent could be considered as belonging to fourteen types. Fifty per cent of the strains of Str. viridans obtained from mouths and throats belonged to types I and II. There was no evidence that significant differences of virulence were connected with special types; invasiveness seems to depend more on the resistance of the host. It would be interesting in view of Colebrook's observation to learn if any of these strains of streptococci are clumped by the standard type-specific serums prepared with hemolytic streptococci.

In support of the contention of Bloomfield and Rantz [59] that scarlet fever is not a disease entity, it appears that erythrogenic toxins made by other bacteria may also cause scarlatiniform rashes. In this respect little attention seems to have been given to earlier work on the staphylococcus, but Aranow and Wood [70] report a case in which the causative staphylococcus produced an erythrogenic toxin which was neutralized by the usual scarlatinal antitoxin. The disease was identical with scarlet fever, yet no beta hemolytic streptococci were isolated.

Rheumatic Fever.—In a fifteen year study of the records of 12,000 patients Cohn and Lingg [71] confirmed most of the previously established concepts of rheumatic fever in regard to its incidence according to age, the frequency of arthritis, myocarditis and chorea at different ages, and the eventual outcome. The peak of incidence is in the eighth year of life. At all ages polyarthritis is the most frequent single manifestation. Before the age of 10 valvular lesions are the first manifestation in 10 per cent of the patients; after 40, in 80 per cent. Ten per cent of the patients lived more than thirty years after the first attack, and 50 per cent died within nine years. The mean duration of life was thirteen years. Recurrences are most prevalent before puberty. The younger the patient at the onset of the disease, the greater is the chance that infection will be severe during the next few years. Less than one half of the children with severe infection survive childhood.

In four publications [72] the results of studies on chemoprophylaxis of rheumatic fever are discussed, with the idea that if predisposing infections with hemolytic streptococci can be prevented, rheumatic fever or its relapses will not occur. Small daily doses of sulfanilamide were given continually to a group of children during the winter months, and in each report the incidence of streptococcic infections and of rheumatic fever was said to be greatly reduced as compared with that in control groups not so treated. Toxic effects occurred in about 15 per cent of the subjects in one series, but were not serious. The results of these studies reemphasize the etiologic importance of group A hemolytic streptococci in rheumatic fever.

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69. Solowey, M.: A Serological Classification of Viridans Streptococci with Special Reference to Those Isolated from Subacute Bacterial Endocarditis, J. Exper. Med. **76**:109-126 (July) 1942.

70. Aranow, H., Jr., and Wood, W. B., Jr.: Staphylococcic Infection Simulating Scarlet Fever, J. A. M. A. **119**:1491-1495 (Aug. 29) 1942.

71. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease: A Statistical Study; I. Onset and Duration of Disease, J. A. M. A. **121**:1-8 (Jan. 2) 1943; II. Manifestations of Rheumatic Activity: Recurrence, Severity of Infection and Prognosis, ibid. **121**:113-117 (Jan. 9) 1943.

72. Hansen, A. E.; Platou, R. V., and Dwan, P. F.: Prolonged Use of Sulfonamide Compound in the Prevention of Rheumatic Recrudescences in Children: Evaluation Based on Four Year Study on Sixty-Four Children, Am. J. Dis. Child. **64**:963-976 (Dec.) 1942. Thomas, C. B.: Prophylactic Treatment of Rheumatic Fever by Sulfanilamide, Bull. New York Acad. Med. **18**:508-526 (Aug.) 1942. Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Investigation **22**:77-85 (Jan.) 1943. Chandler, C. A., and Taussig, H. B.: Sulfanilamide as a Prophylactic Agent in Rheumatic Fever, Bull. Johns Hopkins Hosp. **72**:42-53 (Jan.) 1943.

Similar good results in preventing attacks of rheumatic fever were obtained when acetylsalicylic acid was used in daily doses of 4 to 6 Gm.[73] In only 1 of 47 patients so treated did rheumatic fever develop after a hemolytic streptococcus infection, while 57 of 139 similar but untreated patients had recrudescences. If these results are confirmed, it would seem preferable to use the salicylic acid drugs in place of the sulfonamide compounds because of their relative nontoxicity.

In a clinical study [74] of 271 cases of rheumatic fever in children, the disease in one third of them was at first mistaken for poliomyelitis, osteomyelitis, erythematous or purpuric reactions of the skin, nephritis, sepsis, pneumonia, subacute bacterial endocarditis and other low grade infections. It was unusual that pyogenic arthritis, syphilis, scurvy, serum sickness or trichinosis, which are often mentioned in differential diagnosis, were not suspected in any of the cases studied.

Meningococcic Meningitis.—An epidemic of meningococcic meningitis as severe as the epidemic of 1929 was rampant in the winter of 1942-1943.

Branham [75] finds rabbit antimeningococcus serum to be superior to the horse serum. Refined, concentrated rabbit serum is sometimes ten times as potent as the horse serum now in use. Antiserum is still of value in treating meningococcic meningitis, especially in patients who cannot tolerate sulfonamide compounds. It is preferable always to determine the type of the causative meningococcus and to give specific type antiserum if possible. However, since this is not always possible, polyvalent serum may be used. In all epidemics studied in the last twenty years 90 per cent of the strains have been included in group I.

In searching for a better method by which to identify members of the Neisseria group of cocci Phair and co-workers [76] found chicken serum to be useful. Various strains of meningococci and gonococci injected into chickens evoked highly specific agglutinating serums, which provided a rapid and dependable means of identification.

BACILLARY DISEASES

Bacillary Dysentery.—In the studies of Penner and Bernheim [77] on the genesis of dysentery, the toxins of Bacillus dysenteriae (Shiga) when injected into animals caused a shocklike state with compensating vasoconstriction in the small intestine and formation of a diphtheria-like membrane. The reaction is not specific, as it may be caused by other procedures. Toxin applied directly to the bowel wall caused no harmful local effect until after it had been absorbed. If the same mechanism is operative in human infection, bacillary dysentery is to be regarded not as a local disease of the intestines but as a systemic one with secondary lesions in the intestines. In this case the superiority of sulfaguanidine over the more soluble sulfonamide compounds in the treatment of bacillary dysentery may not be so great as at present supposed. Support for this view is available in Paulley's report,[78] in which sulfapyridine is stated to be preferable to sulfaguanidine in

73. Coburn, A. F., and Moore, L. V.: Salicylate Prophylaxis in Rheumatic Fever, J. Pediat. **21**:180-183 (Aug.) 1942.

74. Hansen, A. E.: Diagnosis of Rheumatic Fever, J. A. M. A. **121**:987-991 (March 27) 1943.

75. Branham, S. A.: Comparison of Rabbit and Horse Serums in Meningococcus Infection, Pub. Health Rep. **58**:478-483 (March 19) 1943.

76. Phair, J. J.; Smith, D. G., and Root, C. M.: Use of Chicken Serum in the Species and Type Identification of Neisseria, Proc. Soc. Exper. Biol. & Med. **52**:72-73 (Feb.) 1943.

77. Penner, A., and Bernheim, A. I.: Studies on the Pathogenesis of Experimental Dysentery Intoxication, J. Exper. Med. **76**:271-282 (Sept.) 1942.

78. Paulley, J. W.: Treatment of Bacillary Dysentery in the Middle East, Lancet **2**:592-594 (Nov. 21) 1942.

treatment. In his experience it is of more importance to maintain a satisfactory amount of the drug in the blood than in the bowel. If the disease is mild, he gives 2 Gm. of sulfapyridine, then 1 Gm. every four hours until a total of 20 Gm. has been given. The average period of disability in his patients was four and two-tenths days. As a commentary on the time-honored custom of giving hydragogues, his patients progressed just as favorably on the "do nothing, plus fluids" regimen. Hardy and his associates[79] also favor the use of the more readily absorbed sulfonamide compounds. Sulfadiazine was the most effective in rapidly controlling massive infections with the Sonne variety of bacilli, and sulfasuxidine (succinylsulfathiazole) was the best in ridding convalescents and passive carriers of Sonne bacilli. In mild cases of dysentery lasting several days no chemotherapeutic effects were noted with succinylsulfathiazole,[79a] as might be expected in disease of such short duration.

Several important detailed epidemiologic investigations were made on dysentery. One[80] concerned the Shiga variety in an outbreak of infection in a rural community, and the others,[81] the Flexner and Sonne types among inmates of an institution. The studies represent an enormous amount of bacteriologic work and bookkeeping, the difficulties of which few who have not engaged in such research can appreciate. In general they reemphasize the importance of direct contact and lack of cleanliness in the spread of the disease. In one study dysentery bacilli were found in 6.6 per cent of 13,000 stools from persons without dysentery. The prevalence of carriers varied from time to time—from none to 26 per cent. The Sonne variety of bacilli were more persistent than others. The ratio of clinical infections to carrier states in one group was as 1:7 for the Flexner variety and as 1:24 for the Sonne variety. Infection with one variety conferred no immunity against another. The probable mode of transmission in most cases is through person to person transmission of fecal pollution. There is every reason to believe that any insect crawling first on infected material and then on food may contaminate it, but only recently have ants been incriminated.[82]

A review of the bacteriologic aspects of dysentery bacilli has been published.[83]

Typhoid Fever.—One of the few reported epidemics of typhoid fever associated with a "small colony variety" of Eberthella typhosus, type E, occurred in Georgia.[84] Apparently large colony variants appeared among the small ones on culture mediums, and their biologic reactions were similar. It is important to know that

79. Hardy, A. V.; Burns, W., and DeCapito, T.: Studies of the Acute Diarrheal Diseases: X Cultural Observations in the Relative Efficiency of Sulfonamides in Shigella Dysenteriae Infections, Pub. Health Rep. **58**:689-693 (April 30) 1943.

79a. Roberts, T. L., and Daniels, W. B.: Succinylsulfathiazole in the Treatment of Bacillary Dysentery, J. A. M. A. **122**:651-653 (July 3) 1943.

80. Caudill, F. W.; Teague, R. E., and Duncan, J. T.: A Rural Shiga Dysentery Epidemic, J. A. M. A. **119**:1402-1406 (Aug. 22) 1942.

81. Hardy, A. V.; Shapiro, R. L.; Chant, H. L., and Siegel, M.: Studies of the Acute Diarrheal Diseases: IX. A. Shigella Dysenteriae Infections Among Institutional Inmates, Pub. Health Rep. **57**:1079-1094 (July 24) 1942. Watt, J.: Hardy, A. V., and DeCapito, T.: IX. B. Shigella Dysenteriae Infections Among Institutional Inmates, ibid. **57**:1095-1102 (July 24) 1942.

82. Griffith, S. D.: Ants as Probable Agents in the Spread of Shigella Infections, Science **96**:271-272 (Sept. 18) 1942.

83. Weil, A. J.: Progress in the Study of Bacillary Dysentery, J. Immunol. **46**:13-46 (Jan.) 1943.

84. Morris, J. F.; Barnes, C. G., and Sellers, T. F.: An Outbreak of Typhoid Fever Due to the Small Colony Variety of Eberthella Typhosus, Am. J. Pub. Health **33**:246-248 (March) 1943.

unusual or variant forms of pathogenic bacteria may cause disease, and laboratory technicians must be aware of their existence so that they will not be discarded as contaminants.

Edwards and Bruner [85] report the classification of 3,000 cultures of Salmonella, among which were 59 types. Practically all strains of human origin may be easily classified by using eight "O" serums in the slide agglutination test. It is gratifying that a numerical system of type nomenclature may eventually supplant the use of other, often unsatisfactory, terms.

Brucellosis.—Because some investigators reported the isolation of brucellas from the lymph nodes in Hodgkin's disease and suggested a possible relationship between the two diseases, Bloomfield [86] restudied the problem. He found that enlargement of superficial lymph nodes was not uncommon in brucellosis, occurring in 58 per cent of 50 cases. Therefore, because of many other similarities between the two diseases, even including the histologic changes in the lymph nodes, it is easy to confuse them. It is unlikely that brucellosis has any connection with Hodgkin's disease. Martin [87] reports that the mediastinal lymph nodes were shown enlarged in roentgenograms in 6 cases of undulant fever. Pressure from these nodes was thought to be the cause of a dry, irritative cough in an occasional case.

Angle and his associates [88] show that it is important to use standardized polyvalent antigens prepared against five to ten strains for the diagnostic serologic tests in brucellosis because of the variations of specificity encountered. Wide variations in agglutination were noted in the different tests even on the same sample of blood.

Tetanus.—According to experience in the British Army,[89] tetanus bacilli are rarely found in the soil in the Middle East but are commonly present in wounds (8.4 per cent). In one group of 18 patients with tetanus 5 had been actively immunized with two or three doses of toxoid, but none had received antitoxin after injury. Of 7 who recovered, none had been immunized. It becomes more and more apparent that while immunization against tetanus is a valuable procedure, it is not always successful in preventing the disease or in lessening its severity. In several papers in the March issue of the *Journal of Clinical Investigation,* Mueller and his associates report the production of tetanus toxin in peptone-free media, and the production and use of toxoid made from it. This method of production is advantageous in eliminating other factors which may give rise to undesirable foreign protein reactions when tetanus toxoid is reinjected for purposes of immunization.

According to Cooke and Jones,[90] the immunity passively obtained with the usual prophylactic dose of 1,500 units of tetanus antitoxin lasts only about three weeks, but that obtained with large doses, e. g., 100,000 units, was demonstrable for eleven weeks. Repeated injections of tetanus toxoid did not produce antitoxic

85. Edwards, P. R., and Bruner, D. W.: The Occurrence and Distribution of Salmonella Types in the United States, J. Infect. Dis. **72**:58-67 (Jan.-Feb.) 1943.

86. Bloomfield, A. L.: Enlargement of the Superficial Lymph Nodes in Brucella Infection, Am. Rev. Tuberc. **45**:741-750 (June) 1942.

87. Martin, W. S.: Mediastinal Glands in Undulant Fever, J. Michigan M. Soc. **41**:1051-1052 (Dec.) 1942.

88. Angle, F. E.; Algie, W. H., and Morgan, D.: Brucellosis: Studies Emphasizing Strain Variation in Serologic Testing, J. Lab. & Clin. Med. **27**:1259-1263 (July) 1942.

89. Boyd, J. S. K., and Maclennan, J. D.: Tetanus in the Middle East, Lancet **2**:745-749 (Dec. 26) 1942.

90. Cooke, J. V., and Jones, F. G.: The Duration of Passive Tetanus Immunity and Its Effects on Active Immunization with Tetanus Toxoid, J. A. M. A. **121**:1201-1209 (April 10) 1943.

immunity within several weeks. Toxoid is probably of value in immediate prophylaxis only after the subject has had previous "sensitizing" injections of toxoid.

Tularemia.—An epizootic of tularemia among beavers in Montana is described.[91] Since these animals did not harbor the usual insect vectors of this disease, the source of the disease is unknown. It is possible that infected field mice living in the vicinity were the source. The beavers may have become infected by living in water polluted with urine or with carcasses of infected mice. Water in several of the streams tested contained Pasteurella tularensis.

Although no one has heretofore prepared an efficient vaccine against tularemia, Foshay and his co-workers [92] now report success. A vaccine prepared by oxidizing the bacilli with nitrous acid apparently gave complete protection to some exposed persons, and in those in whom disease did occur it was mild.

Anthrax.—The controversy as to the best method of treating anthrax is still undecided. Gold [93] reviews 60 cases and concludes that sulfathiazole therapy should be given in preference to other forms of treatment. While in his experience anti-anthrax serum is helpful, the large amounts used often provoke distressing serum sickness, and neoarsphenamine is of little value. These conclusions vary from those previously published by Lucchesi, who also has had extensive experience with the disease. He uses neoarsphenamine in preference to sulfonamide compounds but agrees that antiserum is of value. Both agree that the local lesion should not be molested. It is obviously difficult to gage the comparative value of the various forms of therapy in the absence of control therapeutic tests. It is my feeling that the great majority of patients with anthrax recover without therapy and that the mortality rate is lower than is usually believed. It is almost certain that a person with a small pimple caused by anthrax without constitutional symptoms, and such cases no doubt occur, will not even seek medical advice, and if he does the real nature of the infection may not be recognized without bacteriologic studies. Nevertheless, because of the danger of a mild infection becoming rapidly worse and because of the fatalities which do occur, further attempts to develop efficient specific therapy are desired.

Pertussis.—Protection against whooping cough by the injection of the toxin of Haemophilus pertussis is feasible but this toxin is of no value if used after the disease is established.[94] Dauer,[95] who made a statistical study of pertussis, points out that pertussis vaccine has not been used in a large enough number of persons or for a long enough time to permit judgment of its effect in reducing the mortality rate from the disease. Furthermore, if the mortality rate, which declined spontaneously by 80 per cent in the past fifteen years, continues to decline so rapidly, it will not be possible to prove statistically the value of any prophylactic measure. Since 40 per cent of deaths occur in infants under 6 months of age, vaccination if used would have to be started at an extremely early age, at an age at which the effectiveness of vaccine is not known.

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91. Jellison, W. L.; Kohls, G. M.; Butler, W. J., and Weaver, J. A.: Epizootic Tularemia in the Beaver, Castor Canadensis, and the Contamination of Stream Water with Pasteurella Tularensis, Am. J. Hyg. **36**:168-182 (Sept.) 1942.

92. Foshay, L.; Hesselbrock, W. H.; Wittenberg, H. J., and Rodenberg, A. H.: Vaccine Prophylaxis Against Tularemia in Man, Am. J. Pub. Health **32**:1131-1145 (Oct.) 1942.

93. Gold, H.: Anthrax: A Review of Sixty Cases, with a Report on the Therapeutic Use of Sulfonamide Compounds, Arch. Int. Med. **70**:785-820 (Nov.) 1942.

94. Bullowa, J. G. M., and Alterman, J.: Pertussis Immunity with Toxin and Antitoxin, J. A. M. A. **120**:886-890 (Nov. 21) 1942.

95. Dauer, C. C.: Reported Whooping Cough Morbidity and Mortality in the United States, Pub. Health Rep. **58**:661-672 (April 23) 1943.

Pertussis may result in hemorrhagic, inflammatory and degenerative changes in the cerebrum, a fact which was known years ago and recently reemphasized.[96] The disease in infancy may be the cause of eventual mental derangement, with troublesome problems of behavior and psychoses. Among a group of 500 such children, nearly one half had had pertussis. Diabetes insipidus has also occurred after pertussis.

Two cases of septicemia with Bacterium necrophorus are reported and the literature on the subject reviewed by Buhler, Seely and Dixon.[97]

Tuberculosis.—Ordway and Medlar [98] reopen the controversial question of the significance of tubercle bacilli in the urine. They observed that about 8 per cent of tuberculous patients had tubercle bacilli in the urine and that most of these patients had no clinical evidence of renal tuberculosis. The presence of tubercle bacilli in the urine does not indicate that progressive renal tuberculosis will inevitably follow; healing may occur. Surgical intervention should therefore be delayed until progressive renal destruction has been demonstrated.

Other observers [99] state that a difference of virulence as measured by tests on guinea pigs can be detected in tubercle bacilli isolated from patients with fresh, active disease as compared with those from patients with chronic infection. According to this observation, tubercle bacilli apparently gradually lose their virulence in patients as well as on artificial mediums over long periods. The results need confirmation.

Leprosy.—In an epidemiologic discourse on leprosy McCoy [100] points out the differences in consequences after the disease had been brought to different parts of the United States. For example, in Louisiana, Florida and Texas its importation led to the establishment of permanent foci, while in the midwestern states and in California the disease failed to perpetuate itself. In the latter areas and elsewhere leprosy is of little importance.

In regard to the treatment of leprosy McCoy [101] concludes that chaulmoogra oil and its derivatives are of little or no curative value and that their unpleasant side effects probably outweigh any advantage to the patient that might accrue from their use. He cites similar opinions of a number of other authorities.

Both fleas [102] and ticks [103] were suggested as possible vectors of leprosy.

According to two Cuban dermatologists,[104] a change in the classification of leprosy from the cutaneous, neural and mixed types decided on at recent congresses is desirable. They and many South American leprologists deem it wiser to classify

96. Levine, L. A., and Levy, S.: Personality Changes and Behavior Disorders of Children Following Pertussis, Pub. Health Rep. **58**:890-894 (April 23) 1943.

97. Buhler, V. B.; Seely, C. W., and Dixon, D. D.: Bacterium Necrophorus Septicemia in Man, Am. J. Clin. Path. **12**:380-386 (July) 1942.

98. Ordway, W. H., and Medlar, E. M.: Tuberculous Bacilluria: A Ten Year Study, J. A. M. A. **119**:937-943 (July 18) 1942.

99. Corper, H. J., and Cohn, M. L.: The Presence of Relatively Avirulent Tubercle Bacilli in Pulmonary Tuberculosis in Man, J. A. M. A. **120**:427-431 (Oct. 10) 1942.

100. McCoy, G. W.: Observations on the Epidemiology of Leprosy, Pub. Health Rep. **57**:1935-1943 (Dec. 18) 1942.

101. McCoy, G. W.: Chaulmoogra Oil in the Treatment of Leprosy, Pub. Health Rep. **57**:1727-1733 (Nov. 13) 1942.

102. Muñoz Rivas, G.: Transmission of Leprosy by Fleas, Rev. Fac. de med., Bogotá **10**: 635-679 (April) 1942.

103. Souza Araujo, H. S., cited in Transmission of Leprosy by Ticks, Foreign Letters (Brazil), J. A. M. A. **120**:1053 (Nov. 28) 1942.

104. Pardo-Castello, V., and Tiant, F. R.: Leprosy: The Correlation of Its Clinical, Pathologic, Immunologic and Bacteriologic Aspects, J. A. M. A. **121**:1264-1268 (April 17) 1943.

the disease on a pathologic basis as (*a*) lepromatous, with nodular infiltrative lesions, (*b*) tuberculoid, with infiltrated annular lesions, and (*c*) nonspecific, with macular manifestations of the skin and simple dystrophic neural disorders. Lepromatous lesions are rich in Hansen's bacilli, while in the other two forms bacilli are rare. The lepromin reaction is said to be positive only in patients with the tuberculoid type, but as it is also positive in normal people, it is unreliable as a diagnostic test. The authors' discussion of the reaction is confusing. One wonders if the new classification is actually an improvement over the old and whether it is worth while to give so much attention to clinical classification.

VIRAL DISEASES

"Viral" Pneumonia.—A comprehensive review [105] of the subject of "viral" pneumonia and numerous clinical studies published during the year indicate how widespread the disease or group of diseases is. As reported by Duggan and Powers [106] and by several others,[107] it appeared in epidemic form in numerous military camps, and the incidence there, as elsewhere, often far exceeded that of other known types of pneumonia. In New York the board of health has now required that it be reported. Unfortunately, against the advice of all who have written on the subject, the sulfonamide compounds have been widely and unnecessarily used in its treatment. In one report [108] the undesirable term "sulfonamide-resistant pneumonia" is actually used to describe the disease. In another,[109] an equally bad term, "silent bronchopneumonia," is applied because of the typically delayed appearance of pulmonary signs of pneumonia. The authors appear to be unfamiliar with the literature on the subject. In describing an epidemic in an army camp, Campbell and his associates [109a] criticize the numerous names thus far suggested but add a worse one themselves, "acute bronchiolitis with associated atelectasis." In a small group of cases, according to one report,[110] convalescent serum gave good results in shortening the disease. The report is unconvincing as to the specificity of the effects stated.

As I stated elsewhere,[111] it seems that the disease entity primary atypical pneumonia, commonly called viral pneumonia, appears as a fairly uniform clinical syndrome in two general forms: (*a*) as a sporadic or epidemic, slightly contagious systemic disease with a relatively long incubation period; (*b*) as the severest type of involvement in large epidemics of mild contagious local disease of the respiratory tract with a short incubation period, usually in the cold months. If this

105. Finland, M., and Dingle, J. H.: Virus Pneumonias: I. Pneumonias Associated with Known Nonbacterial Agents: Influenza, Psittacosis and Q Fever, New England J. Med. **227**:342-350 (Aug. 27) 1942; II. Primary Atypical Pneumonias of Unknown Etiology, ibid. **227**:378-385 (Sept. 3) 1942.

106. Duggan, L. B., and Powers, W. L.: An Acute Respiratory Infection Resembling So-Called Acute Pneumonitis: A Report of Forty Cases, J. Lab. & Clin. Med. **28**:524-530 (Jan.) 1943.

107. Dingle, J. H.; Abernathy, T. J.; Badger, G. F.; Buddingh, G. J.; Feller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, W. B.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223-248 (March) 1943.

108. Gsell, O., and Engel, M.: Sulfonamid-resistente Pneumonien, Schweiz. med. Wchnschr. **72**:35-38 (Jan. 10) 1942.

109. Andrus, P. M.: Silent Bronchopneumonia, Canad. M. A. J. **47**:339-344 (Oct.) 1942.

109a. Campbell, T. A.; Strong, P. S.; Grier, G. S., and Lutz, R. G.: Primary Atypical Pneumonia: A Report of Two Hundred Cases at Fort Eustis, J. A. M. A. **122**:723-729 (July 10) 1943.

110. Flexner, M., and Garon, M. L.: Virus Pneumonia: Treatment with Convalescent Blood, Kentucky M. J. **41**:5-13 (Jan.) 1943.

111. Reimann, H. A.: Viral Pneumonias, Bull. New York Acad. Med. **19**:177-182 (March) 1943.

classification is correct, a loose arrangement of the few known causes of the genuine viral types of pneumonia may be given as follows:

Sporadic Nonseasonal Forms	*Epidemic Winter Forms*
Varicella	Influenza A
Vaccinia	Influenza B
Variola	Measles
Psittacosis, ornithosis, ailourosis [112]	Cotton rat infectious virus? [114]
Lymphogranuloma venereum	Guinea pig infectious virus [114]
Lymphatic choriomeningitis	Unknown causes (colds, grip)
Mongoose infectious virus	
Cotton rat infectious virus [114]	
Feline pneumonic virus [113]	
Guinea pig infectious virus? [114a]	
Ill defined and unknown causes	

Four newly discovered viruses have been added to the list of causes of the syndrome commonly called "virus pneumonia," as indicated in the foregoing tabulation, but the cause of the "viral pneumonia" in the majority of the cases, especially of that which occurred in epidemic form in the past winter, is as yet unknown. The four new viruses are described in the four paragraphs that follow.

A virus was obtained by Baker [112] from cats which, according to a preliminary report, has several characteristics that suggest its relation to the psittacosis-ornithosis-meningopneumonitis group discussed in last year's review.[17] If a relationship does appear, and if precedence in nomenclature is permissible, the agent may be named ailourosis virus. Antigen prepared with this virus gave complement fixation in the serum of a number of patients who had atypical pneumonia at the same time that a similar epizootic occurred among cats. The same virus was thought to be responsible in both the human patients and cats, and cross infection may have occurred.

Cats were suspected by Blake, Howard and Tatlock [113] as the source of another virus which may be the cause of pneumonia in man. Evidence suggests that the infection in cats was transmitted to several members of a family, sick at about the same time. Neutralization tests with patients' serum and the cat virus gave suggestive evidence that the same virus caused the disease in both species. The virus could be passed serially through kittens but not through mice, an observation which differentiates it from certain other viruses now related to atypical pneumonia.

Eaton and his associates [114] report the transmission and adaptation of a virus from 6 patients with atypical pneumonia to cotton rats. The virus is apparently not related to other known viruses. It was partially and irregularly neutralized by the serum of patients convalescent from pneumonia. However, rats immunized by inoculation of adapted strains were immune to reinfection with material from a human lung which produced pneumonia in controls, but rats immunized with material from the human lung were only partially resistant to rat strains. In the studies of a commission for the investigation of atypical pneumonia in an army camp,[107] a virus infectious for cotton rats was isolated from 4 patients. Intracytoplasmic inclusion bodies were present in the pneumonic lungs of the rats.

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112. Baker, J. A.: A Virus Obtained from a Pneumonia of Cats and Its Possible Relation to the Cause of Atypical Pneumonia in Man, Science **96**:475-476 (Nov. 20) 1942.

113. Blake, F. G.; Howard, M. E., and Tatlock, H.: Feline Virus Pneumonia and Its Possible Relation to Some Cases of Primary Atypical Pneumonia in Man, Yale J. Biol. & Med. **15**:139-165 (Dec.) 1942.

114. Eaton, M. D.; Meiklejohn, G.; Van Herick, W., and Talbot, J. C.: An Infectious Agent from Cases of Atypical Pneumonia Apparently Transmissible to Cotton Rats, Science **96**:518-519 (Dec. 4) 1942.

Rose and Molloy [114a] established a virus from 7 of 11 patients in recently weaned guinea pigs. The infection could be passed to cotton rats.

Final proof of the relation of each of these viruses to atypical human pneumonia is obviously not at hand, owing to the difficulties and uncertainties involved in the technic now available. But it is at least evident that important knowledge is accruing, and it is hoped that in time the causes of the common forms of viral pneumonia will be discovered.

In addition to the discovery of the "new" viruses, progress has been made in an attempt to clarify problems related to viruses previously reported. For example, Horsfall and his co-workers [115] inoculated sputum and blood from patients with atypical pneumonia into various animals but produced no infection which could be obviously propagated. In 1 case, however, primary inoculation of cotton rats caused pulmonary consolidation, but in subsequent passage the agent was lost. This experience is so much like that of Stokes and Kenny and that of Francis and Magill, who obtained similar results in the first attempts made to study the cause of viral pneumonia by using nasopharyngeal washings and blood from the patients whose cases I reported in 1938, as to suggest that we may have dealt with the same or a similar virus. At any rate, the evidence obtained in the work of Horsfall and his associates suggests that the infective agent is antigenically related to and biologically similar to the pneumonic virus of mice and to the mongoose infectious virus, both previously discovered by him. Here again, because of the difficulties of technic and the irregularities in results, conclusions must be interpreted with caution.

On somewhat more certain ground is work giving evidence of infection with ornithosis virus in human cases of "viral" pneumonia. In my own experience,[116] in 4 of 8 cases infection with the psittacosis-ornithosis group of viruses was suggested by the indirect means of the complement fixation test. Three similar instances are reported by Favour,[117] and a fourth by Stickney and Heilman,[118] who isolated the virus. Eaton and Corey [119] and Smadel [120] found evidence of infection with this group of viruses in about 15 per cent of cases of atypical pneumonia tested. Smadel prefers not to use the term "ornithosis" but to regard the disease as due to a strain of the virus of psittacosis. Andrewes and Mills,[121] who isolated the virus from pigeons in England, are of similar mind. It must be recalled that complement fixation does not specifically indict any one of several viruses each of which reacts similarly, namely, those of psittacosis, ornithosis, meningopneumonitis of mice and lymphogranuloma venereum. To complicate matters more, it has recently been

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114a. Rose, H. M., and Molloy, E.: Observations Concerning the Etiology of Primary Atypical Pneumonia, Science **98**:112-114 (July 30) 1943.

115. Horsfall, F. L.; Curnen, E. C.; Mirick, G. S.; Thomas, L., and Ziegler, J. E.: A Virus Recovered from Patients with Primary Atypical Pneumonia, Science **97**:289-290 (March 26) 1943.

116. Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias with a Brief Résumé of Recent Discoveries, Arch. Int. Med. **70**:513-522 (Oct.) 1942.

117. Favour, C. B.: Ornithosis (Psittacosis): A Report of Three Cases, and a Historical, Clinical and Laboratory Comparison with Human Atypical (Virus) Pneumonia, Am. J. M. Sc. **205**:162-187 (Feb.) 1943.

118. Stickney, J. M., and Heilman, F. R.: The Isolation of a Virus in Atypical Pneumonia, Proc. Staff Meet., Mayo Clin. **17**:369-375 (June 17) 1942.

119. Eaton, M. D., and Corey, M.: Complement-Fixation in Human Pneumonitis with Group-Reactive Virus Antigens, Proc. Soc. Exper. Biol. & Med. **51**:165-168 (Oct.) 1942.

120. Smadel, J. E.: Atypical Pneumonia and Psittacosis, J. Clin. Investigation **22**:57-66 (Jan.) 1943.

121. Andrewes, C. H., and Mills, K. C.: Psittacosis (Ornithosis) Virus in English Pigeons, Lancet **1**:292-293 (March 6) 1943.

shown that the convalescent serums from patients recovered from atypical pneumonia also reacted with the antigens of influenza A, the pneumonic virus of mice, the cat virus reported by Baker and in low dilution with normal tissue antigen.[122] Serum representing other infectious diseases did not give positive reactions to antigen of the pneumonic virus of mice. Ways to simplify the complexities and avoid confusion are proposed.

In another study [123] it was observed that blood samples from the majority of patients with primary atypical pneumonia had cold agglutinins in dilutions of from 1:10 to 1:10,000 at 0 C. It is suggested that the apparent regularity of this peculiar agglutination may be of aid in diagnosis since, according to the authors, it is rarely present in other infections. The same reaction was independently reported by Turner [123a] and subsequently confirmed by others.[123b]

Influenza.—The subject of influenza was recently reviewed in four publications.[124] Additional interesting studies have also been reported. According to Shope,[125] lungworms, common parasites of swine, may serve as intermediate hosts for the virus of swine influenza, which the author believes to be a surviving prototype of the virus of the pandemic influenza of 1918. Apparently lungworms obtain the virus in the pig's lung. Lungworm eggs containing the virus in "masked" form are shed in the pig's feces and are in turn eaten by earthworms. The eggs hatch as larvas in earthworms, which subsequently are eaten by swine. The larvas become lungworms in pig's lungs, thus completing the cycle. The virus in swine usually lies masked and dormant in the worms or in the adjacent lung tissue, but the virus is activated and clinical influenza may develop when some additional provocative factors operate, such as cold, wet weather or some other infection, especially infection with Haemophilus influenzae suis.

Support for his views is given by the epidemiologic behavior of influenza in swine and the demonstration that swine lungworms and earthworms harbor the virus under natural conditions. Instead of direct transmission of the virus from pig to pig by contact, small epidemics often occur simultaneously in different localities, usually in the first four months of the year, as if provoked into activity by wet, cold weather. Field experiments suggest that, instead of the virus going like wildfire from drove to drove and throughout a drove, it is probably widely seeded and dormant before the outbreak and is provoked into activity in the pigs almost

122. Thomas, L.; Curnen, E. C.; Mirick, G. S.; Ziegler, J. E., and Horsfall, F. L.: Complement Fixation with Dissimilar Antigens in Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **52**:121-125 (Feb.) 1943.

123. Peterson, O. L.; Ham, T. H., and Finland, M.: Cold Agglutinins (Autohemagglutinins) in Primary Atypical Pneumonias, Science **97**:167 (Feb. 12) 1943.

123a. Turner, J. C.: Development of Cold Agglutinins in Atypical Pneumonia, Nature, London **151**:419 (April 10) 1943.

123b. Horstmann, D. M., and Tatlock, H.: Cold Agglutinins: A Diagnostic Aid in Certain Types of Primary Atypical Pneumonia, J. A. M. A. **122**:369-371 (Jan. 5) 1943. Turner, J. C.; Nisnewitz, S.; Jackson, E. R., and Berney, R.: Relation of Cold Agglutinins to Atypical Pneumonia, Lancet **1**:765-769 (June 19) 1943.

124. Horsfall, F. L.: Human Influenza, in Virus Diseases, New York, Cornell University Press, 1943, pp. 113-143; The Present Status of the Influenza Problem, J. A. M. A. **120**:284-286 (Sept. 26) 1942. Francis, T.: Factors Conditioning Resistance to Epidemic Influenza, in Harvey Lectures, 1941-1942, Lancaster, Pa., Science Press, 1942, pp. 69-99; A Rationale for Studies in the Control of Epidemic Influenza, Science **97**:229-235 (March 12) 1943.

125. Shope, R. E.: The Swine Lungworm as a Reservoir and Intermediate Host for Swine Influenza Virus III: Factors Influencing Transmission of the Virus and the Provocation of Influenza, J. Exper. Med. **77**:111-126 (Feb.) 1943; The Demonstration of Masked Influenza Virus in Lungworm Larvae and Swine Under Natural Conditions, ibid. **77**:127-137 (Feb.) 1943; Swine Influenza, in Virus Diseases, New York, Cornell University Press, 1943, pp. 85-109.

simultaneously. After the epidemic is over, further cases seldom occur in the following ten months. In searching old literature Shope found much to support the idea that influenza in man may originate at many remote and diverse places at once. It then, of course, spreads secondarily from each focus. The great rapidity of spread may be more apparent than real, therefore, and represents a delusion resulting from the provocation of widely disseminated masked virus by a stimulus common to large geographic areas. Descriptions of pandemics as early as 1806 by Johnson and others show that the disease appeared to spread much faster than human movement could carry it and that this could be accounted for only by assuming that multiple sources of origin existed and erupted simultaneously.

In regard to the possible relationship of the virus of human influenza to that of swine influenza, Hudson, Sigel and Markham [126] used Hirst's technic to show that the swine virus in England is more closely related to the human type A group of viruses than is Shope's swine virus. In a hypothetic discussion Andrewes [127] carries the matter of interepidemic latency of influenza virus further. He suggests that a "basic" virus, which it seems may be represented by Shope's "masked" virus, exists devoid of specific antigen by which it could be recognized, analogous to "degraded" or "rough" forms of certain bacteria. In this state the virus may live as a saprophyte in man or some other host. But by passage from host to host under favorable circumstances it is enabled to increase its antigen so that it changes through several "grades" of increasing specificity and virulence until it can finally be identified as virus A, for example, with ability to invade man and cause epidemics of clinical disease. Andrewes' theory obviously employs the time-honored epidemiologic concept of the gradual increase of virulence by passage through suitable hosts, a concept which in the past decade has been largely discarded as unproved in favor of the evidence that the degree of virulence of a given phase or variation of a bacterium or a virus is more stable and that variations of virulence are better explained by the appearance, spontaneous or otherwise, of variant forms, each possessing different characteristics.

Francis [128] also regards influenza in pandemic form as a modification of a disease caused by a virus similar to those now known, and not, as some would have it, as an unrelated infection arising spontaneously in a population. The forces which induced pandemicity are not known; several factors must be operative. In one localized epidemic [128a] five slightly different antigenic strains of influenza virus were isolated. Evidence is insufficient to indicate whether a number of different stable viruses exist or whether influenza virus is relatively unstable and may be constantly altered by passage through different hosts.

Hirst [129] introduced a simple and reliable agglutinin inhibition test which depends on the fact that influenza virus causes agglutination of chicken erythrocytes and that the addition of the specific immune serum inhibits the agglutination in the presence of the homologous virus but not in that of any heterologous virus. The test gives quantitative data on influenza virus and qualitative data on influenza

126. Hudson, A. P.; Sigel, M. M., and Markham, F. S.: Antigenic Relationship of British Swine Influenza Strains to Standard Human and Swine Influenza Viruses: The Use of Chicken and Ferret Antisera in Red Cell Agglutination, J. Exper. Med. **77**:467-471 (May) 1943.

127. Andrewes, C. H.: Thoughts on the Origin of Influenza Epidemics, Proc. Roy. Soc. Med. **36**:1-10 (Nov.) 1942.

128. Francis, T.: Epidemiology of Influenza, J. A. M. A. **121**:4-7 (May 1) 1943.

128a. Magill, T. P., and Sugg, J. Y.: Antigenically Different Strains of Virus from a Localized Influenza Outbreak, Proc. Soc. Exper. Biol. & Med. **53**:104-106 (June) 1943.

129. Hirst, G. K.: The Quantitative Determination of Influenza Virus and Antibodies by Means of Red Cell Agglutination, J. Exper. Med. **75**:49-64 (Jan.) 1942.

antibodies, similar to the information obtained by other more complicated tests, such as virus neutralization and complement fixation. According to McClelland and Hare,[130] the virus is almost all adsorbed by the red cells, and the adsorbed virus retains its infectivity. It is evident therefore that both influenza and the viral pneumonias affect erythrocytes in different and peculiar manners. Hirst [131] also succeeded in transmitting influenza virus directly from throat washings to chick embryos in 28 of 54 trials.

The size of the pathogenic agent of influenza is said to be much smaller than 100 millimicrons as once stated.[132] The agent as obtained from the infected developing chick embryo by ultracentrifugation is spherical and measures only 11 millimicrons. Influenza virus is thus one of the smallest of pathogenic agents, resembling the viruses of poliomyelitis and foot and mouth disease.

Influenza Vaccine.—Henle, Henle and Stokes [133b] report good results from vaccination against influenza. A group of 72 volunteers, of whom 44 had received formaldehyde-inactivated allantoic fluid vaccine made from three strains of group A virus, was exposed to active influenza A virus by inhalation. Influenza developed in only 1 of the 44 vaccinated persons and in 10 of the 28 children of the control group. Numerous mild or subclinical infections occurred among both the vaccinated and the unvaccinated subjects. The vaccine used in this experiment apparently was specific and of high potency against the strain of virus used for infection, since Bodily and Eaton [134] find that the immune response to single strains of type A influenza virus is often not sufficiently broad to afford protection against other viruses within the A group which may be slightly different in specific reactivity. This view might serve to explain certain failures in adequate protection with vaccine as reported by others. Furthermore, there appears to be a wide variation of specificity of immune response in human beings to any influenza vaccine. In their experience a few persons vaccinated against influenza A had antibodies also for B influenza. This may have been an anamnestic reaction after a previous infection with the B variety.

Mild Infections of the Respiratory Tract.—The publication of Cowen, Diehl and Baker [135] is welcome in combating overzealous commercial advertising concerning the prevention and the treatment of colds with vitamins. In a controlled study, large doses of vitamin C alone or of vitamins A, B_1, B_2, C, D and nicotinic acid had no effect on the number or the severity of infections of the upper portion of the respiratory tract in adults presumably on a reasonably adequate diet. Diehl adds that even members of the control group had fewer colds than those not

130. McClelland, L., and Hare, R.: The Adsorption of Influenza Virus by Red Cells and a New in Vitro Method of Measuring Antibodies for Influenza Virus, Canad. Pub. Health J. **32**:530-538 (Oct.) 1941.

131. Hirst, G. K.: Direct Isolation of Human Influenza in Chick Embryos, J. Immunol. **45**:293-302 (Dec.) 1942.

132. Chambers, L. A.; Henle, W.; Lauffer, M. A., and Anderson, T. F.: Studies in the Nature of the Virus of Influenza: II. The Size of the Infectious Unit in Influenza A, J. Exper. Med. **77**:265-275 (March) 1943.

133. (*a*) Stokes, J., Jr., and Henle, W.: Studies in Methods of Prevention of Epidemic Influenza, J. A. M. A. **120**:16-20 (Sept. 5) 1942. (*b*) Henle, W.; Henle, G., and Stokes, J., Jr.: Demonstration of the Efficacy of Vaccination Against Influenza Type A by Experimental Infection of Human Beings, J. Immunol. **46**:163-175 (March) 1943.

134. Bodily, H. L., and Eaton, M. D.: Specificity of the Antibody Response of Human Beings to Strains of Influenza Virus, J. Immunol. **45**:193-204 (Nov.) 1942.

135. Cowen, D. W.; Diehl, H. S., and Baker, A. B.: Vitamins for the Prevention of Colds, J. A. M. A. **120**:1268-1270 (Dec. 19) 1942.

included in the experiment. Placebos evidently give excellent results, and patients receiving them may give splendid testimonials for anything used to prevent colds.

On the other hand, evidence both clinical and experimental is accumulating that actual deficiency of vitamins, particularly of the vitamin B complex, has much to do with increased susceptibility to infections.[136] In an experimental study, monkeys given a vitamin B–free basic diet were more susceptible to infections with influenza virus and with Str. haemolyticus.

Stokes and Henle [135a] report that the vaporization of propylene glycol in a concentration of 1 to 30 or 40 million parts of air in a convalescent home for children greatly reduced the incidence of infections of the respiratory tract. Infections occurred as usual after the treatment was stopped. In another study,[137] ultraviolet radiation of air in nursery rooms, arranged so that "curtains" of radiation fell between infants, successfully reduced the number of infections of the respiratory tract.

Further evidence that the so-called common cold may be a syndrome of many causes is illustrated in the report of a peculiar infection by Oliphant and Dawber.[138] During April and May 1942, 200 cases occurred in a military barrack. The infection was presumably traced to the arrival of a person who had had bronchitis. Eleven or more days later the epidemic began. It was characterized by fever, nasal discharge, malaise, conjunctivitis, cough, sore throat, pharyngitis, bradycardia and occasionally bloody sputum. Hoarseness was the rule, but little prostration occurred. The pharynx was usually fiery red, and regional adenopathy was present. No shadows appeared in the roentgenographic lung fields, and doubtful pneumonia was present in only 2. The fever lasted one to three days, but cough and pharyngitis persisted a week in most cases. The leukocytes were seldom increased in number. The disease was not caused by the virus of influenza A or B or by any other known agent.

Encephalitis.—Considerable progress has been made in the recognition of various forms of encephalitis and their relationship to one another. For some time after the discovery of the St. Louis type and Eastern and Western types of equine encephalitis, they were regarded as distinct forms, but Hammon [139] classes them together as "arthropod-borne virus encephalitis." However, since the virus of the so-called Russian spring-summer encephalitis and the virus of Japanese encephalitis have also been found in arthropods in the wild state, it seems logical that Hammon should also include these infections in the aforementioned grouping. If this is done, his grouping will lose significance, and it may still be desirable to apply distinctive names to the various related but slightly different neurotropic viruses. Perhaps a numerical or alphabetic nomenclature would be preferable. Geographic terms or terms signifying certain animal or insect hosts are obviously not desirable, since the St. Louis virus has been found elsewhere than near St. Louis, Western equine virus occurs in the East, and the Eastern equine virus was isolated from a patient

136. Saslaw, S.; Schwab, J. L.; Woolpert, O. C., and Wilson, H. E.: Reaction of Monkeys to Experimental Respiratory Infections: VI. Spontaneous and Experimental Infection in Nutritional Deficiency States, Proc. Soc. Exper. Biol. & Med. **51**:391-394 (Dec.) 1942.

137. Robertson, E. C.; Doyle, M. E., and Tisdall, F. F.: Use of Ultraviolet Radiation in Reduction of Respiratory Cross Infections in a Children's Hospital: Final Report, J. A. M. A. **121**:908-914 (March 20) 1943.

138. Oliphant, J. W., and Dawber, T. R.: An Epidemic of Acute Respiratory Infections of Unusual Type, Pub. Health Rep. **57**:993-997 (July 3) 1942.

139. Hammon, W. M.: Encephalitis: Eastern and Western Equine and St. Louis Types, as Observed in 1941 in Washington, Arizona, New Mexico and Texas, J. A. M. A. **121**:560-566 (Feb. 20) 1943.

in Texas. Furthermore, many different mammals and birds may serve as sources of infection. Mosquitoes and ticks have been proved to be vectors of the viruses.[140]

Other interesting observations on the interrelationship and the widespread distribution of neurotropic viruses were made in Africa by Smithburn and Jacobs.[141] A virus called West Nile virus, of human origin, is antigenically related to the viruses of St. Louis encephalitis and Japanese B encephalitis, yet distinct from both of them. An epidemiologic survey revealed all three viruses to be active over broad expanses in Central Africa; thus more objection to the limiting geographic terms now in use is provided. One wonders if evidence of the existence of West Nile virus or an analogue will eventually be found in the United States or in Japan.

Still other apparently widely separated and supposedly unrelated neurotropic virus infections were grouped together as being similar if not identical by immunologic methods and experiments on animals. Casals and Webster [142] show a close relationship between the Russian tick-borne virus of spring-summer encephalitis of man and the tick-borne virus of the encephalitis of sheep called louping ill in Scotland. The broad relationship of the neurotropic stains of viruses seems to be analogous to that of the strains of rickettsias, such as the ones that cause Rocky Mountain spotted fever, São Paulo typhus and other diseases, since relatives of them or they themselves have since been found in widely scattered regions of the world. As another example, tularemia, named for Tulare County in California, has been found to be endemic in Japan and throughout Europe.

Hamsters are susceptible to infection with the viruses of Western, Eastern and West Nile encephalitis and serve as useful animals for the study of the viruses.[143] Electromicrography reveals the virus of Western encephalitis to be composed of spherical or disk-shaped particles about 4 millimicrons in diameter.[144]

The viruses of lymphogranuloma venereum,[145] rubella [146] and herpes simplex [147] were isolated from the spinal fluid of patients with meningoencephalitis. In the case of lymphogranuloma venereum, symptoms of encephalitis were dominant, and the inguinal lymph nodes were only slightly enlarged. Under these circumstances the diagnosis cannot be made clinically but rests on (1) the inoculation of spinal fluid into mice, (2) the complement fixation test made with the patient's serum and the specific antigen, (3) the Frei test and (4) biopsy of a lymph node. In the other

140. Hammon, W. M., and Reeves, W. C.: Culex Tarsalis Coq., a Proven Vector of St. Louis Encephalitis, Proc. Soc. Exper. Biol. & Med. **51**:142-143 (Oct.) 1942. Hammon, W. M.; Reeves, W. C., and Gray, M.: Mosquito Vectors and Inapparent Animal Reservoirs of St. Louis and Western Equine Encephalitis Viruses, Am. J. Pub. Health **33**:201-207 (March) 1943.

141. Smithburn, K. C., and Jacobs, H. R.: Neutralization Tests Against Neurotropic Virus with Sera Collected in Central Africa, J. Immunol. **43**:9-23 (May) 1942. Smithburn, K. C.: Differentiation of West Nile Virus from the Viruses of St. Louis and Japanese B. Encephalitis, ibid. **43**:25-31 (May) 1942.

142. Casals, J., and Webster, L. T.: Close Relation Between Russian Spring-Summer Encephalitis and Louping-Ill Viruses, Science **97**:246-248 (March 12) 1943.

143. Watson, D. W., and Smadel, J. E.: Susceptibility of Hamsters to Peripheral Inoculation of Western, Eastern, and West Nile Encephalitis Viruses, Proc. Soc. Exper. Biol. & Med. **52**:101-104 (Feb.) 1943.

144. Sharp, G. G.; Taylor, A. R.; Beard, D., and Beard, J. V.: Electron Micrography of the Western Strain Equine Encephalomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **51**:206-207 (Nov.) 1942.

145. Sabin, A. B., and Aring, C. D.: Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, J. A. M. A. **120**:1376-1381 (Dec. 26) 1942.

146. Bradford, R. I. C.: Two Cases of Rubella Meningoencephalitis, Lancet **1**:312-313 (March 13) 1943.

147. Armstrong, C.: Herpes Simplex Virus Recovered from the Spinal Fluid of a Suspected Case of Lymphocytic Choriomeningitis, Pub. Health Rep. **58**:16-21 (Jan. 1) 1943.

case, lymphocytic choriomeningitis was suspected, but the virus of herpes simplex was isolated. Reference is made on page 424 to the occurrence of lymphocytic meningoencephalitis in patients with pleurodynia. These examples show that numerous unsuspected known viruses may give rise to forms of encephalitis and, besides, there is evidence from the reports of Price [148] and of Woodland and Smith [149] that outbreaks of encephalitis occur from time to time in which none of the known agents seems to be implicated.

It is hard to decide whether or not reference should be made to the numerous original articles and discussions of other papers on the subject of encephalitis published by E. C. Rosenow during the past year. Practically all deal with the ideas that he has held for years; namely, the relationship of streptococci and their supposed filtrable state to encephalitis and the use of antiserum against these streptococci. New departures in his views are the demonstrations of "streptococcus antigen" and of the streptococci in question from the mud of a lake bottom, from air at a high altitude and from rain and snow in an epidemic area. The "encephalitic type" of streptococci was also isolated from dying fish, and he apparently finds it necessary to inform his readers that the "transmission of encephalitis by bites of mosquitoes in this species was out of the question." [150] Most investigators over the years have found it difficult if not impossible to accept the majority of Rosenow's tenets, but because of the feeling that, after all, "there may be something to it," they have been reluctant to discard them in their entirety as fantastic obfuscation.

Poliomyelitis.—In a discussion of the genesis of poliomyelitis Sabin [151] suggests that the so-called signs of meningeal irritation should be regarded as the early signs of injury of the neurons instead. Some neurons may be completely destroyed; others, partly so, in which partial or complete recovery may occur. The portion of the central nervous system which is involved depends on the neural connections along which the virus spreads from the peripheral source. There is reason to believe that the virus invades from the alimentary tract through the fifth, seventh, ninth and tenth cranial nerves to cause the bulbar form of poliomyelitis. To affect the lower extremities, the virus may traverse the afferent fibers from the intestines by way of the dorsal root ganglions. In the bulbar form of poliomyelitis there is a heavy concentration of neuronal lesions in the medulla, with fewer in the cord; in the spinal type the reverse occurs.

The incubation period of poliomyelitis as far as Casey [152] could measure was from five to thirty-five days, with an average of twelve days.

A crystalline protein fraction which may represent the virus of poliomyelitis, or at least a protein on which it is adsorbed, was obtained by Racker from the brains of infected mice.[153] In other experiments Bourdillon and Moore [154] obtained an apparently "pure" virus by ultracentrifugation.

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148. Price, A. H.: Sporadic Meningoencephalitis of Undetermined Etiology, abstracted, J. Clin. Investigation **21**:629 (Sept.) 1942.

149. Woodland, J. C., and Smith, E. M.: Acute Encephalitis: Mild Epidemic Observed at Station Hospital, Fort Sam Houston, Texas, J. A. M. A. **120**:358-361 (Oct. 3) 1942.

150. Rosenow, E. C.: The Relation of Neurotropic Streptococci to Encephalitis and Encephalitic Virus, Proc. Staff Meet., Mayo Clin. **17**:551-560 (Nov. 4) 1942.

151. Sabin, A. B.: Pathology and Pathogenesis of Human Poliomyelitis, J. A. M. A. **120**: 506-511 (Oct. 17) 1942.

152. Casey, A. E.: The Incubation Period in Epidemic Poliomyelitis, J. A. M. A. **120**:805-807 (Nov. 14) 1942.

153. Racker, E.: Crystallization of a Protein from Poliomyelitis Infected Mouse Brain, Science **96**:364-365 (Oct. 16) 1942.

154. Bourdillon, J., and Moore, D. H.: Attempts at Purification of a Murine Strain of Human Poliomyelitis Virus, Science **96**:541-542 (Dec. 11) 1942.

Dauer has some discouraging things to say about recent studies on poliomyelitis: In spite of all the research in the past twenty years, little new information has accrued; the manner of person to person transmission is unknown; there is insufficient evidence to incriminate water as a medium of conveyance of practical importance, and there is no proof that insects may serve as vectors or reservoirs or that reservoirs of infection exist in lower animals.[154a]

Apropos of Rosenow's numerous publications on the subject of poliomyelitis, the same remarks as were made under the heading "Encephalitis" apply. In a recent paper [155] he reports the use of a cutaneous test for the diagnosis of poliomyelitis and as a guide for the amount of "poliomyelitis antistreptococcic" serum to be used in treatment. His view that a specific streptococcus is the cause of poliomyelitis is at variance with practically all other evidence.

Epidemic Keratoconjunctivitis.—During the summer of 1941 there was an outbreak of epidemic keratoconjunctivitis in Hawaii chiefly among artisans and others engaged in war work. By early autumn the infection had been carried to California, where a similar occupational group was involved. The peak of the epidemic occurred in January 1942. Since then the infection has appeared in the eastern part of the United States, where it also reached epidemic proportions. As usually happens when unfamiliar epidemics occur, it was at first believed to be a "new" disease, but records suggest that similar ones had been reported since 1890 in Europe and the Orient. It is of especial importance at present because it causes disability lasting from one to five weeks among workers and others essential to the war effort.

In a study of 80 cases in New York, Sanders and his group [156] succeeded in isolating a filtrable virus in 2 of 9 cases. The virus was apparently identical with one previously obtained in similar cases and was neutralized by the serum of a patient who had recovered from the infection. Furthermore, the demonstration of neutralizing antibodies in the blood of other similar patients adds support to the causative relation of the virus to the disease. These observations await further confirmation.

The infection is apparently spread by contact with infected material and is favored by irritation of the conjunctiva by abrasive dust, intense light or other irritants. The incubation period lasts from five to twelve days. One eye is usually affected. The local symptoms are those of intense inflammation, but in from 25 to 50 per cent of patients, more or less severe systemic symptoms occur. Preauricular adenitis is common. Vision is often impaired by corneal changes which for the most part eventually heal without defect. Sulfonamide compounds are said by some to be "almost" specific,[157] and in a few cases the use of "convalescent" serum from patients recovered from the infection seemed to cause clinical improvement, but it is probable that in this as in other forms of conjunctivitis spontaneous

154a. Dauer, C. C.: Poliomyelitis in the United States in 1942 and a Summary of Its Prevalence from 1933 to 1942 Inclusive, Pub. Health Rep. **58**:937-949 (June 18) 1943.

155. Rosenow, E. C.: A Diagnostic Cutaneous Reaction in Acute Poliomyelitis, Proc. Staff Meet., Mayo Clin. **18**:118-128 (April 21) 1943.

156. Sanders, M., and Alexander, R. C.: Epidemic Keratoconjunctivitis: I. Isolation and Identification of a Filterable Virus, J. Exper. Med. **77**:71-93 (Jan.) 1943. Sanders, M.; Gulliver, F. D.; Forchheimer, L. L., and Alexander, R. C.: Epidemic Keratoconjunctivitis: Clinical and Experimental Study of an Outbreak in New York City; Further Observations on the Specific Relationship Between a Virus and the Disease, J. A. M. A. **121**:250-255 (Jan. 23) 1943.

157. Braley, A. E., and Sanders, M.: Treatment of Epidemic Keratoconjunctivitis: Preliminary Report of Ten Cases, J. A. M. A. **121**:999-1000 (March 27) 1943.

recovery without therapy is the rule. According to circular letter no. 14 of the Surgeon General of the Army "there is no specific therapy."

To prevent the disease from spreading, patients should be strictly isolated, and physicians in contact with the disease should use great care to avoid carrying the infection to others.

Yellow Fever.—Although jaundice no longer seems to occur after vaccination against yellow fever, the cause of that which formerly appeared has never been determined with certainty.[158] It is the consensus that the human serum that was a part of the vaccine then used carried a contaminating infectious agent. However, because of otherwise unexplained variations in the incidence of jaundice in equivalently vaccinated persons, the possibility of some extrinsic environmental factor also entered the discussion. The jaundice resembled "catarrhal jaundice" clinically but differed in its long incubation period and its predilection for adults. The vaccine as prepared now is composed only of an aqueous extract of chick embryos infected with "attenuated" 17 D strain of yellow fever virus.[159] It contains considerably more antigen than the older serum-containing vaccine.

Interesting in respect to the probability that the serum caused the jaundice is the study of Beeson,[160] who collected older literature concerning the development of jaundice in patients treated for various reasons by injection of human plasma, serum or lymph and added 7 cases of his own. The resulting jaundice resembled the so-called catarrhal form but had an "incubation period" of from one to seven months, like that which followed vaccination against yellow fever.

Fox and his co-workers [161] in Brazil report 199 cases of encephalitis after vaccinating 55,000 persons against yellow fever. To explain this untoward effect the authors, not wishing to ascribe its cause to some adventitious factor, suggest that a variation occurred in the virus composing a certain lot of vaccine which rendered the vaccine neurotropic. It has always seemed to me that a similar explanation suited the problem of jaundice, but no evidence for it is forthcoming.

Fox and Cabral [162] demonstrated that in the great majority of vaccinated adults the protective action persisted for four years. The duration of relatively strong immunity was much shorter in young persons and disappeared in 10 per cent of them after three years. Children apparently do not react antigenically as well as adults and seem to require vaccination at shorter intervals.

Other Viral Diseases.—The relationship between herpes zoster and varicella is still uncertain. Many believe the two diseases to be caused by unrelated agents, while others believe them to be closely related, assuming that the same virus has variant forms, one causing one and the second the other disease. Garland [163] adds evidence in support of the latter view by reporting 3 cases in which varicella

158. Fox, J. P.; Manso, C.; Penna, H. A., and Madureira Pará: Observations on the Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever, Am. J. Hyg. **36**:68-116 (July) 1942.

159. Hargett, M. V.; Burruss, H. W., and Donovan, A.: Aqueous-Base Yellow Fever Vaccine, Pub. Health Rep. **58**:505-512 (March 26) 1943.

160. Beeson, P. B.: Jaundice Occurring One or Two Months After Transfusion of Blood or Plasma: Report of Seven Cases, J. A. M. A. **121**:1332-1334 (April 24) 1943.

161. Fox, J. P.; Lennette, E. H.; Manso, C., and Souza Aguiar, J. R.: Encephalitis in Man Following Vaccination with 17 D Yellow Fever Virus, Am. J. Hyg. **36**:117-142 (Sept.) 1942.

162. Fox, J. P., and Cabral, A. S.: Duration of Immunity Following Vaccination with the 17 D Strain of Yellow Fever Virus, Am. J. Hyg. **37**:93-102 (Jan.) 1943.

163. Garland, J.: Varicella Following Exposure to Herpes Zoster, New England J. Med. **228**:336-337 (March 18) 1943.

developed fourteen days after exposure to a patient with typical herpes zoster. Many others have previously reported the reverse, namely, herpes zoster occurring during and after outbreaks of varicella.

In an outbreak of smallpox in Glasgow, Scotland, an obscure febrile condition developed in 40 of 92 persons who had been in close contact with the disease.[164] All of them were vaccinated after contact, and the febrile reaction occurred from six to thirteen days afterward. In 30 vaccine was the cause; in 2 the cause was smallpox; in the remaining 8 it was probably smallpox, but the latter was so atypical and mild that it would ordinarily not be diagnosed as such. Evidence is therefore presumptive that in an epidemic a proportion of the patients will have a mild type of smallpox or that in these patients vaccination has modified the severity of the attack.

Smallpox was at its lowest ebb in the United States in 1941, with only 1,432 cases reported. A small outbreak occurred in central Pennsylvania in 1942.

In Gallagher's[165] experience in a boys' school specific immune globin as used to prevent measles was far from reliable. In 14 boys the presumed adequate dosage failed even to modify the severity of the disease. The degree of protection in the treated group as compared with an untreated control group failed to give evidence of its efficiency in the age group 13 to 18.

During the last five years a filtrable virus has been shown to be the cause of rubella, or German measles. An increase in the number of neurologic symptoms in the form of neuritis and encephalitis has also been noted. Habel[166] injected nasal washings obtained from patients early in the disease into 41 monkeys and observed that a rash appeared in 12 animals. The rash with leukopenia, relative lymphocytosis and slight fever were the only evidences of infection. Reinoculation of monkeys several weeks later showed that specific immunity had developed in only 2 of 7 animals. No cross immunity to rubeola was evident.

The virus of rabies was isolated from the brain of a patient in whom the infection was not suspected during life.[167] The antemortem diagnosis was psychoneurosis and acute anxiety. After the diagnosis was corrected, further inquiry revealed a history of the patient having been bitten by a dog.

Andrewes and his associates[167a] tested the therapeutic effects of 115 agents, including penicillin, on several viral infections. None had any beneficial effect except the sulfonamide compounds, which influenced lymphogranuloma venereum.

RICKETTSIAL DISEASES

Typhus fever was contracted by 12 workers in a laboratory, probably by inhaling infective droplets during intranasal inoculation of mice with the murine strain of typhus rickettsias.[168] It was disappointing to learn that each of these workers

164. Napier, W., and Insh, A. M.: Febrile Reactions Among Smallpox Contacts, Lancet **2**:483-484 (Oct. 24) 1942.

165. Gallagher, J. R.: Inefficiency of Immune Globulin in the Prophylaxis of Measles During Adolescence, Am. J. M. Sc. **203**:880-882 (June) 1942.

166. Habel, K.: Transmission of Rubella to Macacus Mulatta Monkeys, Pub. Health Rep. **57**:1126-1139 (July 31) 1942.

167. Schaeffer, M., and Leider, A. G.: Recovery of Rabies Virus from the Brain of an Undiagnosed Case, J. Lab. & Clin. Med. **27**:1263-1267 (July) 1942.

167a. Andrewes, C. H.; King, H., and van den Ende, M.: Chemotherapeutic Experiments with the Viruses of Influenza A, Lymphogranuloma Venereum and Vaccinia, J. Path. & Bact. **55**:173-181 (April) 1943.

168. van den Ende, M.; Stuart-Harris, C. H.; Harries, E. H. R., and Steigman, A. J.: Laboratory Infections with Murine Typhus, Lancet **1**:328-332 (March 13) 1943.

had been vaccinated either with the Castaneda vaccine, composed of killed murine typhus rickettsias, or the Cox type of vaccine, composed of killed epidemic typhus rickettsias, a short time prior to infection. On the other hand, it is possible that the vaccine lessened the severity of the disease, since only 3 patients had moderately severe and the rest mild typhus and may not have been recognized as having typhus had the disease not been in mind.

A similar experience was reported [169] from an American laboratory where two workers previously immunized with three and four doses, respectively, of Cox yolk sac vaccine contracted a mild form of epidemic typhus, one while harvesting egg cultures, the other by accidentally splashing virus into her eye. In both cases the disease was mild and could easily have been mistaken for influenza had not the history been so clear.

Castaneda [170] ascribes the failure of vaccine to give adequate protection in his experience to lack of specificity of vaccine made with murine strains against infection with the epidemic strain. By adding antigen of the epidemic strain to the murine vaccine, a more potent vaccine was devised.

Nearly 3,700 cases of typhus were reported in the United States in 1942, numbers of them from California, where the infection was thought not to occur; however, 229 cases have appeared there since 1916.[171] It is believed that probably not more than 20 per cent of cases are reported, so that the disease is no doubt far more prevalent than the statistics lead one to believe.[172]

During experimental studies to determine the incidence of natural typhus infection among wild rats in Savannah, Ga.,[173] guinea pigs inoculated with rat tissues often died. In searching for the cause of death, obviously not caused by typhus, toxoplasma was found. Nearly 9 per cent of the rats studied were infected with this protozoan agent.

Other Rickettsial Infections.—South American workers, who unfortunately call a form of spotted fever "Brazillian typhus," show that dogs may be artificially infected with the agent and that natural infection occurs as well.[174] Dogs and the ticks which infest them may therefore serve as important sources of infection. Many outbreaks occur in households in which dogs, dog ticks and bedbugs are found to be infected. Since dogs are also incriminated in fièvre boutonneuse, or Mediterranean spotted fever, it is suggested that they may be natural carriers of the disease in the United States. A tick, Amblyomma americanum, known to be a vector of spotted fever in South America, is now for the first time believed to be a natural vector in this country.[175] In a small outbreak of spotted fever in Texas, ticks of this species alone were present.[176] Infected nymphs of Amblyomma

169. Gold, H., and Fitzpatrick, F.: Typhus Fever in a Previously Vaccinated Laboratory Worker, J. A. M. A. **119**:1415-1416 (Aug. 22) 1942.

170. Castaneda, M. R.: Bivalent Typhus Vaccine of High Immunizing Value, Science **96**:304 (Sept. 25) 1942.

171. Halverson, W. L.: Typhus Fever in California, California & West. Med. **51**:196-200 (Sept.) 1942.

172. Eskey, C. R.: Murine Typhus Fever Control, Pub. Health Rep. **58**:631-638 (April 16) 1943.

173. Perrin, T. L.; Brigham, G. D., and Pickens, E. G.: Toxoplasmosis in Wild Rats, J. Infect. Dis. **72**:91-96 (Jan.-Feb.) 1943.

174. Dogs as Healthy Carriers of Brazilian Typhus, Foreign Letters, J. A. M. A. **121**:65-66 (Jan. 2) 1943.

175. Parker, R. R.; Kohls, G. M., and Steinhaus, E. A.: Rocky Mountain Spotted Fever: Spontaneous Infection in the Tick Amblyomma Americanum, Pub. Health Rep. **58**:721-729 (May 7) 1943.

176. Anigstein, L., and Bader, M. N.: New Epidemiological Aspect of Spotted Fever in the Gulf Coast of Texas, Science **96**:357-358 (Oct. 16) 1942.

were also found in Oklahoma. In previous experience in South America a tick of a species of Amblyomma harboring spotted fever was taken from a pet dog.

A brief clinical discussion of trench fever has been published.[177] A case of Q fever was reported from South Carolina,[178] the diagnosis of which is even more doubtful than that of the case described in Montana in 1941. The only evidence of Q fever was a specific complement fixation test positive in the low dilution 1:4. Experimental studies on Q fever [179] showed that the causative rickettsias persisted for a month or more in various tissues after the animals had recovered from the disease.

Philip [180] calls attention to the confusion which has arisen in the nomenclature of pathogenic rickettsias and properly recommends the adherence to accepted taxonomic procedure. According to Steinhaus and Parker,[180a] several sulfonamide compounds, atabrine and tyrothricin (an extract of Bacillus brevis of Dubos) had little or no therapeutic effect in experimental Rocky Mountain spotted fever.

FUNGOUS DISEASES

Coccidioidomycosis.—Because of certain similarities of pulmonary tuberculosis and coccidioidomycosis, with regard both to the acute stage and to the end results in the lungs, with roentgenographic evidence of cysts and areas of calcification, error in diagnosis has no doubt often occurred.[181] In studying large groups of Indians who reacted negatively to the tuberculin test despite roentgenograms of the lungs which showed shadows suggestive of healed tuberculosis, Aronson and his associates [182] suspected that coccidioidomycosis may have been the cause of this phenomenon. In different groups tested with coccidioidin, injected intradermally, the incidence of positive reactions varied greatly from place to place—from none to 94 per cent. It is very likely that in many of these persons who failed to react to tuberculin, infection with the fungus Coccidioides immitis may have been the cause of the calcified pulmonary nodules.

In studies to determine how widespread infection with this fungus is and whether it is being "spread" by human or other carriers, Schenken and Palik [183] concluded that the great majority of cases were in, or originated in, California, Texas, Arizona and New Mexico. In only 5 cases was the source of infection apparently outside this area. Cases described in Minnesota and Virginia were rejected because of lack of proof of the diagnosis. It is fairly certain that the infection is not spreading and that local factors which favor the existence of the fungus control the incidence of infection in persons and in animals residing in these areas.

177. Hurst, A.: Trench Fever, Brit. M. J. **2**:318-320 (Sept. 12) 1942.

178. Zemp, F. E.: Q Fever, J. A. M. A. **121**:828-829 (March 13) 1943.

179. Parker, R. R., and Steinhaus, E. A.: American and Australian Q Fevers: Persistence of Infectious Agents in Guinea Pig Tissues After Defervescence, Pub. Health Rep. **58**:523-527 (March 26) 1943.

180. Philip, C. B.: Nomenclature of the Pathogenic Rickettsiae, Am. J. Hyg. **37**:301-309 (May) 1943.

180a. Steinhaus, E. A., and Parker, R. R.: Experimental Rocky Mountain Spotted Fever: Results of Treatment with Certain Drugs, Pub. Health Rep. **58**:351-352 (Feb. 26) 1943.

181. Winn, W. A., and Johnson, G. H.: Primary Coccidioidomycosis: A Roentgenographic Study of Forty Cases, Ann. Int. Med. **17**:407-422 (Sept.) 1942.

182. Aronson, J. D.; Saylor, R. M., and Parr, E. I.: Relationship of Coccidioidomycosis to Calcified Pulmonary Nodules, Arch. Path. **34**:31-72 (July) 1942.

183. Schenken, J. R., and Palik, E. E.: Coccidioidomycosis in States Other than California with Report of a Case in Louisiana, Arch. Path. **34**:484-494 (Sept.) 1942.

On the other hand, Aronson and Gallagher [184] in testing boys in a school in Massachusetts found 17 of 680 students reacting positively to coccidioidin. Of these, 8 had never been west of the Mississippi River. Five of the 17 failed to react to tuberculin and had calcified areas in their lungs. Whether the positive reactors actually had had coccidioidomycosis, and, if so, where they were infected, is unknown.

In another case of chronic pneumonitis, supposedly tuberculosis, Baldwin [185] isolated an acid-fast chromogenic bacillus which was not virulent for guinea pigs, rabbits or mice. It is obvious that certain patients who have tuberculosis-like chronic pulmonary diseases may be infected with agents other than the tubercle bacillus, and careful bacteriologic investigations should be made in all doubtful cases. It is also evident that pathologists cannot always make a final diagnosis of tuberculosis by the demonstration of tubercles alone. There are many causes of tubercle formation besides Mycobacterium tuberculosis.

Emmons and Ashburn [186] present further epidemiologic data on coccidioidomycosis. A high percentage of rodents in endemic areas are infected with the fungus. Because of this, they are regarded as a reservoir of infection important in the dissemination of the infection to man. However, it seems to me that rodents, like man, which live in an endemic area are merely incidentally infected because of intimate exposure to a fungus which grows in local vegetation of soil and do not necessarily play a role in spreading the disease to other places where the fungus cannot grow. In regions where man has acquired infection, cattle, dogs and sheep may also harbor the fungus.[187]

Emmons and Ashburn isolated a hitherto undescribed fundus from rodents which they call Haplosporangium parvum n. sp. This fungus causes granulomatous lesions and may also cause disease in human beings. Cutaneous tests made with extracts of this fungus gave positive reactions in many persons who also reacted positively to coccidioidin. The two fungi may be related. Furthermore, cultural characteristics of H. parvum are similar to those of Blastomyces dermatitidis and Histoplasma capsulatum, both of which are pathogenic for man.

Trichophytosis or "Athlete's Foot."—Much nonsense has been published on this subject, and thousands of dollars have been wasted as a result of commercial advertising and subsequent use of a variety of remedies for its treatment. According to a recent view,[188] the condition is seldom contagious and is chiefly caused by improper care of the feet. It is brought about by chafing and maceration of the skin resulting from continued moisture, particularly during warm weather, which favor the growth and invasion of the fungus habitually present. Cleanliness and properly fitting ventilated shoes are of far more importance in preventing the condition than are the numerous remedies for its treatment.

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184. Aronson, J. D., and Gallagher, J. R.: Sensitivity to Coccidioidin Among Boys in an Eastern Preparatory School, Am. J. Pub. Health **32**:636-639 (June) 1942.

185. Baldwin, E. R.: Non-Pathogenic Acid-Fast Bacilli: I. A Case of Chronic Pneumonitis Associated with a Non-Pathogenic Acid-Fast Bacillus, Am. Rev. Tuberc. **45**:756-761 (June) 1942.

186. Emmons, C. W., and Ashburn, L. L.: The Isolation of Haplosporangium Parvum N. Sp. and Coccidioides Immitis from Wild Rodents: Their Relationship to Coccidioidomycosis, Pub. Health Rep. **57**:1715-1727 (Nov. 13) 1942.

187. Stiles, G. W., and Davis, C. L.: Coccidioidal Granuloma (Coccidioidomycosis): Its Incidence in Man and Animals and Its Diagnosis in Animals, J. A. M. A. **119**:765-769 (July) 1942.

188. Sulzberger, M. B.; Baer, R. L., and Hecht, R.: Common Fungous Infections of the Feet and Groins: Negligible Role of Exposure in Causing Attacks, Arch. Dermat. & Syph. **45**:670-675 (April) 1942.

Dogs, in addition to being sources of infection for the fungous diseases histoplasmosis and coccidioidomycosis, are also possible sources for Blastomyces dermatitidis, according to Foshay and Madden.[189]

A ringworm-like infection of the skin in children who had played together and with kittens has been reported.[190] Examination of one of the kittens showed it to be infected with the fungus Microsporon lanosum.

A rare case of infection resembling subacute bacterial endocarditis was caused by Histoplasma capsulatum.[190a]

MISCELLANEOUS INFECTIONS

Leptospirosis.—Since the value of convalescent serum in the treatment of Weil's disease is so uncertain, Larson [191] tested the effects of serotherapy in infected mice. Serum from convalescent patients and immune serum prepared by inoculating rabbits with Leptospira icterohaemorrhagiae were used. The protective antibodies were in the globulin fraction and could be concentrated by suitable means. Both forms of serum prevent death in young mice if given on or before the fourth day after infection.

Trichinosis.—In a discussion of the modern aspects of trichinosis, Wright [192] points out how misleading much of the earlier information is, particularly in regard to symptoms. Trichinosis varies greatly in its clinical manifestations, depending on the number of larvas ingested, on reinfections and on the general condition of the host. The so-called typical clinical picture described in textbooks is more the exception than the rule. Large surveys indicate that about 16 per cent of people in this country are infected with Trichinella. It is believed that the incidence can be reduced by feeding hogs cooked rather than raw garbage.

In 2 cases of trichinosis of my own,[193] studied over many months, the typical microscopic lesions and the clinical picture of periarteritis nodosa developed. These later disappeared, and chronic nephritis developed, which in 1 case was fatal. The appearance of the lesions of periarteritis nodosa suggested that they were incited by trichinosis and were allergic in nature, in turn suggesting that trichinosis may be one of the causes of periarteritis nodosa.

A serologically active polysaccharide, which may be helpful in diagnostic tests, was obtained from Trichinella.[194]

Schistosomiasis.—In an article giving the latest information on schistosomiasis of the Manson or intestinal type, Koppisch [195] points out how important it will be for physicians in this country and elsewhere who have had no experience with it to be able to recognize the disease. Beyond doubt a certain percentage of the military

189. Foshay, L., and Madden, A. G.: The Dog as a Natural Host for Blastomyces Dermatitidis, Am. J. Trop. Med. **22**:565-569 (Sept.) 1942.

190. Botvinick, I.; Peck, S. M., and Schwartz, L.: An Outbreak of Microsporon Lanosum Infection from a Kitten, Pub. Health Rep. **58**:317-319 (Feb. 19) 1943.

190a. Broders, A. C.; Dochat, G. R.; Herrell, W. E., and Vaughn, L. D.: Histoplasmosis Producing Vegetative Endocarditis: Review of Literature with Report of a Case, J. A. M. A. **122**:489-492 (June 19) 1943.

191. Larson, C. L.: Treatment of Young White Mice Infected with Leptospira Icterohemorrhagiae with Immune Serum, Pub. Health Rep. **58**:10-15 (Jan. 1) 1943.

192. Wright, W. A.: A Consideration of the Clinical and Public Health Aspects of Trichinosis, Journal-Lancet **62**:389-393 (Nov.) 1942.

193. Reimann, H. A.; Price, A. H., and Herbut, P. A.: Trichinosis and Periarteritis Nodosa: Differential Diagnosis; Possible Relationship, J. A. M. A. **122**:274-279 (May 29) 1943.

194. Melcher, L. R., and Campbell, D. H.: A Serologically Active Polysaccharide from Trichinella Spiralis, Science **96**:431-432 (Nov. 6) 1942.

195. Koppisch, E.: Manson's Schistosomiasis, J. A. M. A. **121**:936-942 (March 20) 1943.

personnel who serve in regions where the disease is endemic will contract it and return home infected. The disease must be diagnosed promptly and specifically treated before it causes irreparable cirrhosis of the liver or other injury, and before the ova escape to establish endemic foci in this country. Although, according to the author, none of the planorbids or mollusks which are capable of acting as intermediate hosts for these schistosomes occur in the United States, it must be remembered that in 1941 Penner [196] found in a Minnesota pond a strain of Schistosomatium douthitti with which he was able to infect monkeys. Only further study will show whether the certain mollusks which occur in this country may harbor other pathogenic schistosomes.

Two cases of imported schistosomiasis (Schistosoma haematobium) were reported from Michigan.[197] The authors refer to several other cases in the United States.

In a preliminary report Anderson describes the cultivation of micro-organisms resembling Donovan bodies from patients with venereal lymphogranuloma.[197a]

Malaria.—Coggeshall [198] calls attention to the danger of malaria becoming widespread in the United States after the return of troops who have been infected elsewhere. Throughout the country important anopheline mosquito vectors are potential transmitters of infection from patients with imported malaria or from healthy carriers, to say nothing of the possibility of the introduction of other dangerous varieties of mosquitoes. The latter accident occurred in Brazil when Anopheles gambiae was accidentally introduced and eventually caused more than 14,000 deaths from malaria before it was eradicated. The author warns that methods designed to control malaria by curbing the larval or adult development of the mosquito, by attempts to prevent mosquito bites in man and by attempts to prevent or cure the disease with drugs have all failed in their purpose. It is disappointing to learn that atabrine (now officially recognized as quinacrine hydrochloride U. S. P.), like quinine, is not curative, but simply controls the acute attack, and if a person succeeds in throwing off the infection, he does so by his own defense mechanism, not as a result of chemotherapy. In one series of cases in Africa, clinical attacks of malaria occurred in 45 per cent of those who were receiving a supposedly adequate prophylactic dose of the drug. The author does not refer to the use of sulfonamide compounds.

Pleurodynia.—An outbreak of 166 cases of pleurodynia occurred in Brooklyn in July 1943.[199] Either the disease differed in certain respects from that described in previous reports or attention was focused on symptoms previously disregarded. The most important differences were the frequency of pharyngitis (75 per cent of cases) and the evidence of meningoencephalitis, which was noted in 5 adult patients and was characterized by typical clinical signs and symptoms and lymphocytes in the spinal fluid. The prominent symptoms in most cases were the usual ones, namely, fever and severe pain in the upper part of the abdomen or the lower part

196. Penner, L. R.: The Possibilities of Systemic Infection with Dermatitis-Producing Schistosomes, Science **93**:327-328 (April 4) 1941.

197. Blum, B. B., and Lilga, H. V.: Schistosomiasis Infection: Report of Two Cases Found in Northern Michigan, J. A. M. A. **121**:125-126 (Jan. 9) 1943.

197a. Anderson, K.: The Cultivation from Granuloma Inguinale of a Microorganism Having the Characteristics of Donovan Bodies in the Yolk Sac of Chick Embryos, Science **97**:560-561 (June 18) 1943.

198. Coggeshall, L. T.: Malaria as a World Menace, J. A. M. A. **121**:8-11 (May 1) 1943.

199. Howard, T.; Weymuller, C. A.; Edson, J.; Ittner, E.; Watson, J., and Cassidy, M.: Epidemic Pleurodynia in Brooklyn in the Summer of 1942, J. A. M. A. **121**:925-929 (March 20) 1943.

of the chest, in both places sufficiently severe to embarrass breathing or to suggest some acute abdominal infection. Convulsions were common in infants. Recoveries were prompt, often within one or two days, but recurrences were common. Aside from pain, which sometimes persisted for weeks, there were no sequels.

The third case of human infection with Pasteurella pseudotuberculosis in the United States has been reported.[200] The bacterium was isolated from the blood of a patient who recovered from the disease.

The first case of tick paralysis to be reported from the eastern part of the United States occurred in New York in a child of 3.[201] During the course of the disease a partly engorged dog tick was found attached to the scalp. On its removal "the disappearance of the patient's symptoms was most dramatic." It is difficult to understand how so instantaneous a cure is possible.

A puzzling disease known as gin fever, Monday fever, Mill fever or byssinosis has long been noted among employees in cotton mills and among those who inhale the dust of jute, grain, flax and hemp. After hundreds of cases occurred in the summer of 1941, Neal and his co-workers,[202] studying the problem, concluded that a short gram-negative bacillus belonging to the genus Aerobacter was the causative agent. It is found chiefly in low grade, stained cotton and is inhaled. The endotoxin it liberates apparently causes disease. The disease begins several hours after exposure with a chill or chilliness, fever, cough, headache, conjunctival irritation and fatigue and lasts four or five days. Intradermal tests with filtrates of the bacillus cause specific hypersensitive inflammatory lesions.

Bradley [203] describes the outbreaks of epidemic nausea and vomiting in several English schools. The disease appeared to be contagious, with an incubation period of two to seven days. The chief symptoms were vomiting, nausea, dizziness, headache and diarrhea. Fever seldom lasted more than twenty-four hours. The disease might be mistaken for food poisoning, but no evidence of the latter was found. All bacteriologic studies gave negative results. An unknown virus was suggested as a possible cause. It may be mentioned in passing that no filtrable virus has ever been incriminated as a cause of gastroenteritis. It is highly probable that some exist that may cause this disease and may account for certain epidemics of so-called dysentery of unknown cause.

Two apparently "new" exanthematous diseases have been reported. In Connecticut, Blake and his associates [204] have studied 11 cases in the last five years. The disease was characterized by fever, no prostration, a reddish brown eruption, general swelling of the lymphatic nodes, splenomegaly and leukopenia with relative lymphocytosis. It occurred chiefly in the spring and fall. The rash appeared from two to fourteen days, usually about six days, after the onset. Chills, chilliness, mild sore throat, conjunctivitis and photophobia were noted at times. All tests for known infections gave negative results.

The other disease was observed in Georgia (and elsewhere) among persons who had bathed a week before in a muddy pool apparently polluted with animal

200. Snyder, G. A. C., and Vogel, N. J.: Human Infection by Pasteurella Pseudotuberculosis: Report of Case with Recovery, Northwest Med. **42**:14-15 (Jan.) 1943.

201. DeSanctis, A. G., and di Sant'Agnese, P. A.: Tick Paralysis: Report of a Case in New York, J. A. M. A. **122**:86-88 (May 8) 1943.

202. Neal, P. A.; Schneiter, R., and Caminita, B. H.: Report on Acute Illness Among Rural Mattress Makers Using Low Grade Cotton, J. A. M. A. **119**:1074-1082 (Aug. 1) 1942.

203. Bradley, W. H.: Epidemic Nausea and Vomiting, Brit. M. J. **1**:309-312 (March 13) 1943.

204. Blake, F. G.; Welt, L. G., and Craige, B.: Apparently Undescribed Infectious Exanthem, Yale J. Biol. & Med. **14**:573-580 (July) 1942.

refuse.[205] Thirty-five cases occurred in August 1940. The onset was sudden, with severe headache, postorbital pain, chilliness and sweating. Lumbar pains, nausea and vomiting, arthralgia and constipation were common. The most striking feature was a fine red measles-like rash chiefly over the anterior aspects of the legs, especially over the tibias, but noted once on the chest and the abdomen. The exanthem appeared about the sixth day and lasted one or two days. The fever ranged from 100.6 to 104 F., but the pulse was relatively slow. In only 1 case was a swollen lymph node found, an epitrochlear node. The disease lasted about a week. The leukocytes were normal in quantity and quality, and biologic tests for the typhoid group, undulant fever, typhus and tularemia gave negative results. Tests for leptospirosis, or Weil's disease, which I should consider of importance in this instance, were not mentioned, nor was schistosomiasis, although a less likely possibility, discussed. Daniels and Grennan[206] describe a similar disease which they call "pretibial fever," a rather meaningless term which in common parlance means as much as "hot shins" might.

It will be of interest if in both cases the diseases eventually prove to be newly recognized entities or unusual forms of already known infections.

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205. Bowdoin, C. D.: A New Disease Entity (?) J. M. A. Georgia **31**:437-438 (Dec.) 1942.

206. Daniels, W. B., and Grennan, H. A.: Pretibial Fever: An Obscure Disease, J. A. M. A. **122**:361-365 (June 5) 1943.

Book Reviews

Allergy. By Erich Urbach, M.D., with the collaboration of Philip M. Gottlieb, M.D. Price, $12.00. Pp. 1073, with 396 illustrations. New York: Grune & Stratton, 1943.

This is a rather exhaustive treatise on clinical allergy, containing most of the orthodox information and arrangements found in a number of other books on this phase of medicine and having, in addition, some of the individualistic views and terminology of the author. The text is divided into three parts: Part 1 deals with the fundamentals of allergy; part 2 discusses the etiologic agents, and part 3 concerns itself with the manifestations and therapy. A large part of the voluminous literature on allergy has been incorporated in the text, for which the specialist and the advanced student in allergy will be grateful. One who has had little practical experience in clinical allergy may become confused by the enormous detail and insufficient evaluation of this material.

A valuable contribution in this book is a complete chapter on allergy with relation to certain infectious diseases. Another feature is the exposition of Urbach's new terminology and classification of the phenomena of hypersensitiveness. He uses the term "pathergy" to designate all altered reactivity. The term allergy or "allergic pathergy" is confined by him to specific altered reaction in which specific antibodies are found. Other terms prominent in the book are "parallergy," "metallergy," "nonallergic pathergy" and "allergization." The concepts represented by these names are not new, although the terminology has been adopted by the author. It is to be regretted that in the chapter on diagnosis the author saw fit to devote only one paragraph to the important phase of history taking. In the chapter on treatment Urbach summarizes his previously published work on "propeptan" treatment, which consists of the use of specific peptones prior to feeding allergenic foods. Although this work has in general failed to receive recognition in this country, it is gratifying to know that the details are available for further experimentation. Urbach favors oral pollen therapy, a stand which would be challenged by American allergists of large experience. Some points in technical details are contrary to accepted ideas. For example, the inference that the allergist should confine himself to ten to twenty scratches at one sitting has no logical background and would, if followed, interfere with efficiency in the practice of allergy. The admonition that alcohol must not be used on the skin prior to making scratches has no clinical foundation.

The book is replete with illustrations, mainly photographs, having a total of 396. Many of these are excellent reproductions of various conditions and particularly cutaneous lesions. Nevertheless, on making a careful appraisal of all the illustrations, the reviewer finds that the majority are repetitious, do not possess teaching value or are entirely superfluous. One or two examples may be mentioned. Figure 118 depicts angioneurotic edema due to egg allergy; figure 119, due to fish; figure 341, due to strawberries; figure 342, due to sardines; figure 343, due to acetylsalicylic acid; figure 344, due to enteritis; etc. Figures 328 to 339, inclusive, and other photographs in various portions of the book show patients with urticaria due to various causes, such as strawberries, milk, bacteria, intestinal parasites, enteritis, colitis, dental infection, effort, sweat and mental factors. It certainly would have sufficed to give two or three morphologic variations and merely to mention the various causes.

Although deletion of numerous photographs and reduction in the size would have improved the book, nevertheless, the author and his collaborator have produced a commendable text on allergy and are to be congratulated particularly for their thoroughness. Urbach's "Allergy" will find a place on the shelves of those who have had sufficient experience to evaluate this subject. For others, such as those general practitioners, pediatricians, internists and rhinologists who may have only a secondary interest in allergy, this exposition will probably be too voluminous and complex.

The Hemorrhagic Diseases and the Physiology of Hemostasis. By Armand J. Quick, M.D., Ph.D. Price, $5.00. Pp. 340. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

In 1941 Quick delivered the Beaumont lectures. This book represents an extension and expansion of these lectures and brings up to date the experimental and theoretic aspects of hemostasis. This is the main subject matter of the monograph, but it is most logically correlated with the hemorrhagic diseases and the bleeding tendency in general.

Following the introductory chapter there are six chapters dealing respectively with thrombin, prothrombin, fibrinogen, thromboplastin, blood platelets and anticoagulants. The succeeding six chapters have to do with the clinical manifestations of the diseases which are characterized by a tendency to bleed. The discussion of thrombopenic purpura is noteworthy, and it can be

said that the other chapters on clinical manifestations are excellent. Particularly notable and of extreme value to clinicians, pediatricians and surgeons is chapter 12, which deals with the hemorrhagic diathesis associated with avitaminosis K, obstructive jaundice, biliary fistula and damage to the liver. Chapter 13 is a continuation of the discussion of the same diathesis in which the hemorrhagic diseases of the newborn and toxic sweet clover disease are presented.

For the laboratory worker there is a well organized appendix which outlines the various procedures and technics employed in the study of the hemorrhagic diseases.

The author is well qualified to discuss hemostasis. He is one of the outstanding students of the subject and is widely recognized as an authority. He has presented his work and the work of others clearly and has satisfactorily evaluated the important clinical and laboratory features of the several diseases that he discusses.

It might not be amiss to state that the book itself is an outstanding example of the art of bookmaking. Since an excellent grade of paper has been used, the illustrations are clearcut. The numerous references are printed in relatively large type and can be readily consulted. Altogether, the monograph may be praised most highly, both for its content and for its appearance.

Urology in General Practice. By Nelse F. Ockerblad, M.D., and Hjalmar E. Carlson, M.D. Price, $4.00. Pp. 383. Chicago: The Year Book Publishers, Inc., 1943.

Simplification of medical procedure is highly commendable. In this book an attempt has been made, based on almost forty years of experience in the urologic field, to simplify present urologic methods. The procedures outlined are practical and should direct the medical student and the general practitioner to a solution of the more common urologic problems. Little discussion is presented. The advantages and disadvantages of the procedures recommended are not discussed, and no comparison is made between the methods advised and other available procedures. The brevity of the presentation is an aid to quick assimilation, but at times the discussion is so limited that little specific information can be obtained. This is especially true of the section on urologic diagnosis, in which incontinence, uremia and polyuria are discussed. Most of the topics, however, are dealt with concisely and in sufficient detail to be informative. The chapter on the uses and dangers of catheters and sounds is presented in such a way that much assistance can be obtained in the practical handling of these instruments. The section on sterility presents a definite, practical plan for the diagnosis of this condition in either the male or the female. The language used is conversational and frequently nonmedical.

The book is nicely printed and bound and is to be recommended as a quick and practical guide to those not acquainted with the more common urologic methods.

Whooping Cough. By Joseph H. Lapin, M.D. Price, $4.50. Pp. 237, with 25 tables and 24 plates. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

This handsome monograph includes a systematic discussion of whooping cough in all its phases. History, epidemiology, pathology, symptoms, treatment, etc., are thoroughly discussed, and the bibliographies are adequate. The recent work on preventive vaccination is analyzed, and in general the publisher's statement that the book is based on "extensive clinical experience and exhaustive study of the literature" seems to be justified.